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Referral Pattern of Urological Malignancy in Indonesia

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Summary—In the 10 years between 1976 and 1985, 202,111 patients were admitted to Hasan Sadikin Hospital, Bandung. Of these, 211 (0.1%) had a urological malignancy. Bladder tumours were commonest and constituted 39%. Testicular tumours accounted for 24%, renal tumours 18%, prostatic carcinoma 13% and penile tumours 6%.

Bladder tumours were predominantly transitional cell carcinoma; only 2 patients presented with squamous cell tumours associated with bladder stones. In 50 cases of testicular tumour, 72% were seminomas and 22% were embryonal cell carcinomas. Wilms' tumours accounted for 21 of 39 cases of renal malignancy; the other 18 were renal carcinomas.

No urogenital malignant disease was sufficiently common to be included in either the top 10 malignancy list or the male top 10 malignant diseases in Indonesia.

The importance of epidemiological information about cancer is well known but information is lacking from many developing countries. Indonesia is a developing country with a population of approximately 170 million and, by area, is the third largest country in the world. At the present time it has no population-based cancer registry and the only data available are those from hospital-based registries. The purpose of this study was to present data from a hospital-based registry in Bandung, an industrialised city of 3 million people on the island of Java.

Patients and Methods

All patients presenting with genitourinary malignant tumours in the 10-year period 1976 to 1985 at Hasan Sadikin Hospital were reviewed in relation to the total number of admissions and the total number of malignancies.

Results

Between 1976 and 1985 there were 202,111 admissions and 211 cases (0.104%) of urological malignancy were identified. The classification of the cancers is shown in Table 1 and is based on the World Health Organization (1978) International Classification of Diseases.

The age of the patient in relation to the tumour type is shown in Table 2. All bladder tumours were transitional cell carcinomas except for 2 which were

Table 1 Pattern of Malignancy in Urology

	No. of patients	*%*
Bladder tumour	83	39.3
Testicular	50	23.7
Renal	39	18.5
Prostatic	27	12.8
Penile	12	5.7
Total	211	100

Table 2 Site of Tumours and Age of Patients (years)

Site	*M/F*	*15*	*15–24*	*25–44*	*45–64*	*65*	*Total*	*M+F*
Bladder	M	—	—	11	22	18	51	83
	F	—	—	9	14	9	32	
Testicular	M	7	6	15	18	4	50	50
Renal	M	11	4	3	9	—	27	39
	F	9	—	1	—	2	12	
Prostatic	M	—	—	2	5	20	27	27
Penile	M	—	—	6	6	—	12	12
Total		27	10	47	74	53	211	211

Accepted for publication 18 March 1988

squamous cell carcinomas associated with bladder stone. Most were in an advanced stage (T3–T4). Of 50 cases of testicular tumour, 36 (72%) were seminomas and 11 (22%) were embryonal cell carcinomas. Nephroblastomas were found in 21 (53.9%) of 39 cases of renal tumour and the remaining 18 were renal carcinomas.

The ranking of urological tumours in relation to all tumours is shown in Table 3. The 10 most frequent cancers in this hospital are shown in Table 4 and the 10 most frequent cancers in men are listed in Table 5.

Table 3 Position of Urological Malignancy among other Malignant Diseases

Position ranking	*Tumour*	*No of patients*	*%*
25	Bladder	83	0.041
27	Testicular	50	0.025
31	Renal	39	0.019
34	Prostatic	27	0.013
42	Penile	12	0.006
Total		212	0.104

Table 4 The 10 most Frequent Malignant Diseases

Tumour	*%*
Cervix	0.934
Breast	0.609
Lymphatic system	0.488
Nasopharynx	0.279
Ovarian	0.269
Integument	0.255
Soft tissue	0.184
Ear, nose, sinus	0.178
Rectal	0.146
Lung, trachea, bronchus	0.143

Table 5 The 10 most Frequent Malignancies in the Male

Tumour	*%*
Lymphatic system	0.295
Nasopharynx	0.202
Ear, nose, sinus	0.124
Lung, trachea, bronchus	0.112
Integument	0.108
Soft tissue	0.094
Rectal	0.081
Metastatic neck glands	0.069
Blood	0.051
Larynx	0.039

Discussion

The most reliable cancer register is population-based but such a register does not exist in Indonesia. A hospital-based register is much less accurate for several reasons: for example, the population attending a particular hospital may not represent the whole because some people live far away from the hospital, others may not be able to afford hospital care and also because a particular hospital may attract a selected population because of its reputation and its staff. Nevertheless, a hospital-based registry can give useful information and may be particularly important if there is a changing pattern of disease with time.

Another way to look at cancer prevalence is by annual mortality statistics (Skeet, 1982). Two of our patients have died from prostatic carcinoma, 2 from bladder carcinoma, 1 from Wilms' tumour and 1 from renal carcinoma. These figures are almost certainly a gross underestimate because of lack of follow-up patients. Many patients who are dying will not return to hospital care in Indonesia and prefer to die at home; this means that cancer mortality statistics are neither a helpful nor a practical method of gathering information in Indonesia at the present time.

Another problem with the registration of cancer in Indonesia is the diverse nature of the country. The island of Java is heavily populated. Most of it is agricultural but the cities, including Bandung, are industrialised. Many of the other Indonesian islands are less populated and in some places there are large tracts of tropical rain forest with a persisting tribal society. This means that cancer data from one part of Indonesia (or indeed one part of Java) cannot necessarily be extrapolated to represent the whole country.

Most cancer registry data have come from developed countries and it is clear that the picture in Bandung is very different from that in Western Europe. In the United Kingdom the most common cancers in the male in order of frequency are lung, skin, prostate, stomach and bladder (Wilson, 1987) and this is obviously different from our male cancers (Table 5). Our results are, however, similar to those from other hospital-based registries in two other large cities in Java, namely Jakarta and Surabaya. We have no explanation for this apparent difference in the incidence of urological cancers in Indonesia but plan to continue our hospital register as this provides information which may be useful when planning medical resources and may in the longer term provide useful information about the impact of further economic and industrial development on urological cancer. This may be particularly important for bladder cancer because of the known association between bladder cancer and certain industrial processes.

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Analgesic Effect and Tolerance of Voltaren and Ketogan in Acute Renal or Ureteric Colic

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Summary—Fifty-six patients with renal or ureteric colic were entered into a randomised, prospective, double-blind investigation of the analgesic efficacy and tolerance of Voltaren^{R} versus Ketogan^{R}, both administered intramuscularly. There were no significant differences regarding pain-relief but side effects were fewer in patients treated with Voltaren.

The traditional treatment for acute renal and ureteric colic is the use of morphia alone or in combination with spasmolytics. In recent years prostaglandin synthesis inhibitors have been used more frequently (Orloff and Zusman, 1978; Morrison, 1980; Sjödin, 1981).

In this study we compared the efficacy and tolerance of diclofenac (Voltaren), a prostaglandin synthesis inhibitor, and ketobemidonechloride 3-dimethylamino-1,1-diphenylbuten-(1) hydro-chloride (Ketogan), a morphine derivative combined with a spasmolytic agent.

Patients and Methods

A total of 88 patients suffering from acute renal or ureteric colic were included in a randomised, double-blind investigation of the analgesic efficacy and tolerance of Voltaren and Ketogan. Intravenous urography was done in all patients. Those in whom neither stones nor signs of newly passed stone were observed (7 in the Voltaren group and 8 in the Ketogan group) were excluded. Administrative reasons, such as loss of or insufficient recorded data, led to the withdrawal of 14 patients (7 in the Voltaren and 7 in the Ketogan group) and 3 patients were withdrawn for other reasons; 1 had greatly increased s-amylase, another suffered anaphylactic shock during penicillin treatment and the third had a ruptured aortic aneurysm. Thus 32 patients were excluded and 56 patients, 17 women and 39 men aged 20 to 83 years (median 55) were assessed.

The patients were treated with matching ampoules (3 ml) containing Voltaren (75 mg diclofenac) or Ketogan (7.5 mg ketobemidonechloride and 37.5 mg 3-dimethylamino-1, 1-diphenylbuten-(1) hydrochloride). Both preparations were given intramuscularly.

Evaluation. The patients themselves recorded their pain before and during treatment on a visual analogue scale (VAS) with the extreme points "no pain" and "the pain cannot get worse" (1–100 mm). Vomiting, nausea and other systemic disturbances were also registered before and during treatment. Reduction of fluid intake was not prescribed.

Table Details of Patients

Data	*Ketogan (n=27)*	*Voltaren (n=29)*	*Test**
Age (years)	54 (21–69)‡	57 (20–83)‡	NS
Weight (kg)	76 (42–135)‡	73 (65–120)‡	NS
Ratio of men to women	1.7:1	3.14:1	NS
Patients with earlier stone attacks	14	12	NS

*Mann-Whitney and chi^2 test ‡ Median (range).

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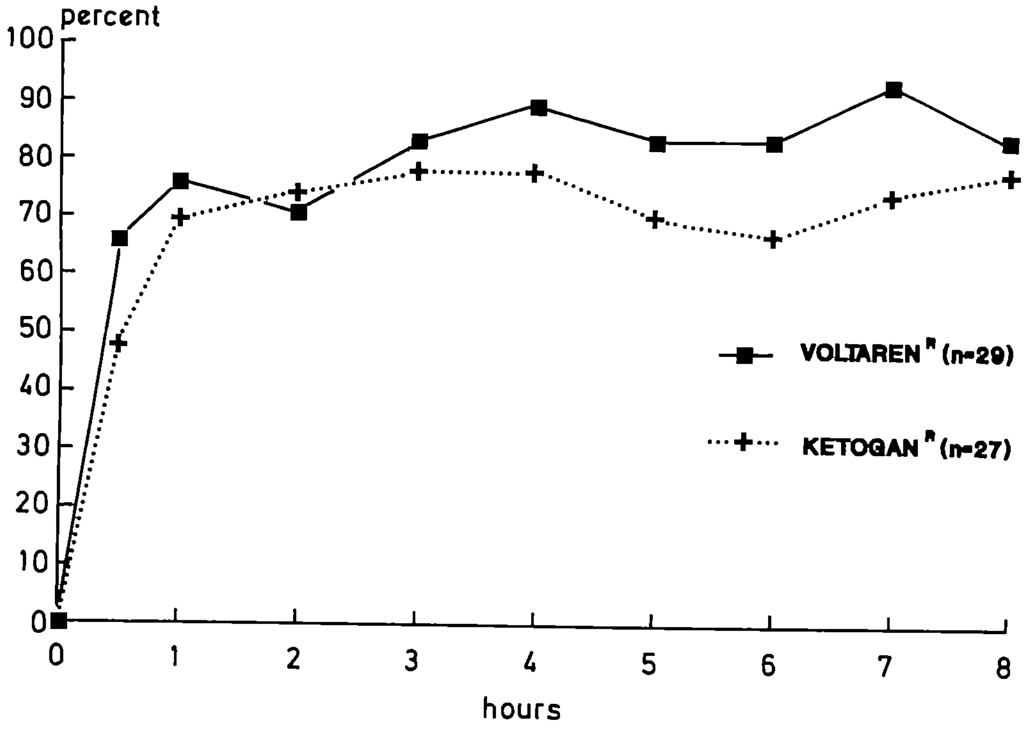

Fig. 1 Percentage of patients who were pain-free within the first 8 h.

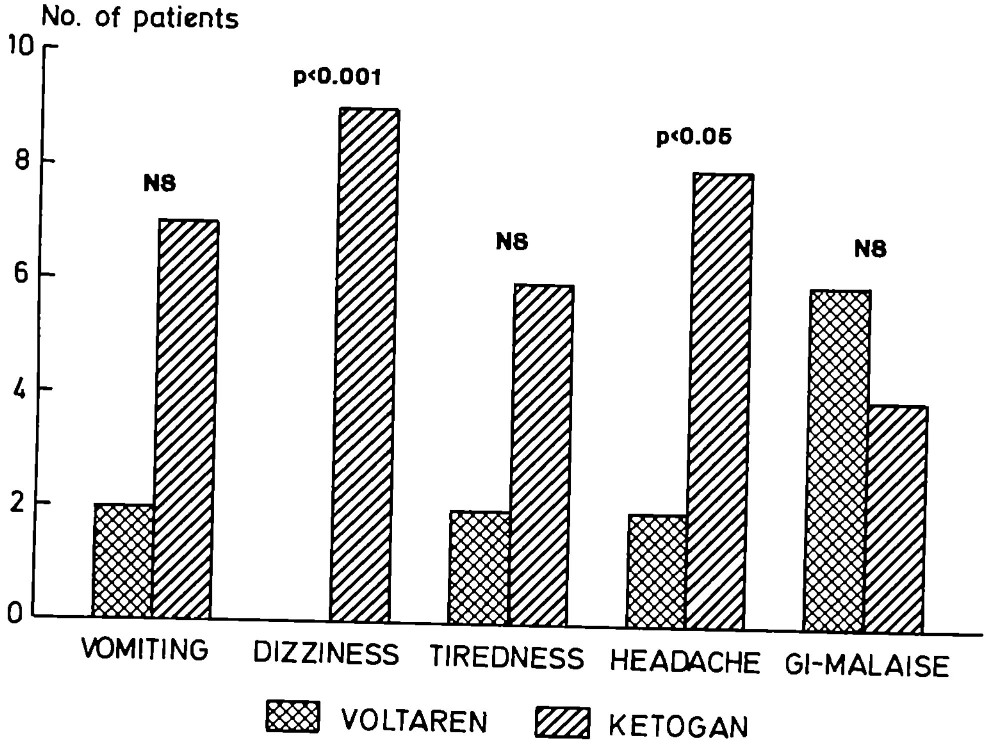

Fig. 2 Tolerance

Results

Voltaren was given to 29 patients and Ketogan to 27. No differences were seen between the two groups in terms of age, weight, sex and number of previous stone episodes (Table). At the start of treatment no differences were seen between the groups with regard to pain, nausea or radiological findings.

Pain-relieving effect. The patients' assessment of pain on the visual analogue scale at set times showed no difference between the two preparations. Similarly, the number of patients without pain (VAS $\leqslant$ 10 mm + patients asleep) after 30 min, 1 h, *etc.*, showed no significant difference between the two groups (Fig. 1).

The intake of fluid was the same in both groups (Voltaren: median 1.9 l, range 0.2–3.5; Ketogan: median 1.9 l, range 0–3.7).

Tolerance. Significantly more patients treated with Ketogan developed headache ($P = 0.027$) and dizziness/euphoria ($P < 0.001$). With regard to tiredness, drowsiness or gastroenterological disturbances and vomiting, no significant differences were found between the two groups (Fig. 2).

Discussion

This investigation showed that both Ketogan and Voltaren are effective in the treatment of acute renal or ureteric colic. It confirms previous investigations (Lundstam *et al.*, 1982). There was no difference with regard to pain relief between the two preparations, but Voltaren gave significantly fewer side effects, which makes it a good alternative to conventional analgesics when treating patients with renal or ureteric colic.

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Urine Microscopy and Culture in the Selection of Patients for Urinary Tract Investigation

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Summary—In a 1-year laboratory-based study the validity of certain findings on microscopy and culture of mid-stream urine specimens as predictive of the presence of structural or functional abnormalities of the urinary tract was tested. During 1986, infection was diagnosed in 12,705 specimens sent to the laboratory by general practitioners; in the light of the findings a comment suggesting the possibility of underlying urinary tract pathology was appended to the reports of specimens from 652 patients. Data were available from the investigation of 233 of these patients. The percentage in whom abnormalities were detected considerably exceeded that reported from studies of bacteriuric children and of adult women with symptoms. It is suggested that the use of these criteria may assist clinicians to select, from the very large number of patients who suffer from urinary tract infection, those who require investigation.

Urinary tract infection (UTI) is diagnosed bacteriologically in an ever increasing number of patients. There are several reasons for this. Over the past 30 years the adverse consequences of UTI have become more clearly recognised (Lancet, 1979). Parallel with this recognition have come the wider availability of laboratory diagnostic services and more extensive postgraduate training of general practitioners. A balance must now be struck between the need to detect underlying urinary tract pathology, whether structural or functional, the need to spare patients unnecessary, expensive and unpleasant investigations, and the need to use limited health care resources wisely.

Figures are available for the number of urinary tract abnormalities detected in children identified as bacteriuric on screening (Kunin, 1970; Newcastle ASB Research Group, 1975) or as a result of symptoms (Hallett *et al.*, 1976), and in adult women presenting with symptomatic UTI. In the majority of studies of children, all underwent intravenous urography (IVU) and micturating cystourethrography (MCU); in a study of adult women by Fowler and Pulaski (1981) the patients underwent cystoscopy in addition to IVU and MCU. The findings of all of these studies indicate that urinary tract abnormalities are found in only a minority of bacteriuric patients. In recent years paediatricians, and specialists working in the field of UTI in adults, have developed their own protocols for deciding upon the indications for urinary tract investigations in individual patients. These vary considerably and there is, at present, no widely accepted consensus. General practitioners have been given no guidance in the selection of patients who should be subjected to investigation.

Twenty years' experience of clinical and laboratory work in the field of UTI has left the author with a strong impression that certain clinical and bacteriological findings are associated with urinary tract pathology. With the purpose of testing the validity of these impressions a laboratory-based study was undertaken during 1986.

Patients and Methods

Throughout 1986 the following comment: "The findings suggest the possibility of underlying urinary tract pathology" (reason given in parentheses)

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was appended by the authorising doctor to selected mid-stream (MSU) reports on specimens sent to the laboratory by general practitioners. The indications for the use of the comment were as follows: mixed infection confirmed by a fresh carefully collected repeat specimen; infection persisting after appropriate treatment; infection with an organism resistant to at least 3 of the 4 commonly used antibacterial agents which are tested in the laboratory (nitrofurantoin, sulphonamide, amoxycillin, co-trimoxazole); recurrent infection in children or adult males; infection with an unusual organism (the organisms included in this category were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas* spp., *Haemophilus influenzae*, *Corynebacterium* spp., *Gardnerella vaginalis*, and streptococci other than *S. faecalis* and *S. agalactiae*) confirmed in a fresh carefully collected repeat specimen; resistant or persistent *Proteus* infection or a single *Proteus* infection in girls aged less than 15 years, in whom *Proteus* infection is rare (Maskell and Pead, 1976); UTI when the request form stated that the patient had fever or acute pyelonephritis; apparently "sterile" pyuria confirmed on culture of a fresh carefully collected repeat specimen; haematuria in the absence of infection in children; UTI in children when enuresis was mentioned on the request form. In general, the comment was not appended to reports on specimens from elderly people (over 65); there were, however, a few exceptions when the indication seemed particularly strong.

Using the computer system of the two Portsmouth hospitals, it was possible to ascertain whether patients to whose reports the comment had been appended had been referred for investigation. After seeking the consent of the appropriate clinical colleagues the results of any investigations were recorded. The laboratory serves a wide area and it was not possible to obtain information about patients who may have been referred to other hospitals.

Results

During 1986, 38,641 urine specimens were sent to the laboratory by general practitioners. Factors taken into account in diagnosing infection in these specimens included bacterial count, purity of growth, presence of pyuria (defined as >10 cells/µl uncentrifuged urine) and relevant clinical information including the age and sex of the patient. Infection was diagnosed in 12,705 specimens (33%) and the comment was appended to 652 reports (5% of those in which infection was reported). At the time of writing, data were available on 233 patients, 111 children and 122 adults, who were referred for investigation as a result of the comment.

Table 1 shows the reasons for the comment in children and relates them to the number of patients found to have abnormalities. Table 2 gives the same information for adults. The number of indications for the comment exceeds the number of patients because two or more indications were present in some patients.

A total of 45 abnormalities was found in 42 (38%) of the 111 children, 2 boys and 40 girls. They were: vesicoureteric reflux (18), pyelonephritic scarring (11), duplex kidneys and ureters (3), renal calculi (3), bladder abnormalities including diverticula, trabeculation and large residual volumes (8), traumatic rupture of the kidney (1) and glomerulonephritis (1). No abnormalities were identified in the other 69 children, but 33 of them were investigated only by ultrasonography and/or plain abdominal radiography, 5 had MCU with/without ultrasonography and 5 had isotope renography only. If the findings in the 73 children who underwent either IVU or isotope renography are analysed separately, abnormalities were found in 42 (58%).

The 122 adults investigated included only 5 men and 10 women over the age of 65; 69 abnormalities were found in 64 patients (52%), 13 men and 51 women. They were: calculi (16), chronic pyelonephritic scarring (10), hydronephrosis and/or hydroureter (13), neoplasms (9), duplex kidney and/

Table 1 Relationship of a Finding of Urinary Tract Abnormality to the Indication for the Comment in 111 Children (<15 years)

*Reason for comment**	*Male*	*Female*
Mixed infection	0	6 (3)
Persistent infection	2 (1)	6 (4)
Infection with resistant organism	3 (1)	19 (10)
Recurrent infection	1	15 (8)
Infection with unusual organism	2	18 (7)
Resistant or persistent *Proteus* infection (or single *Proteus* infection in a girl)	5	12 (2)
UTI with fever or acute pyelonephritis	1	7 (4)
"Sterile" pyuria	2 (1)	34 (16)
Haematuria in absence of infection	0	2 (2)
Infection with enuresis	0	10 (3)
Total number of patients	13 (2)	98 (40)

*For precise definition of reasons see text.

Figures in parentheses = number of patients found to have abnormalities.

Table 2 Relationship of a Finding of Urinary Tract Abnormality to the Indication for the Comment in 122 adults

	15–55 years		*Over 55 years*	
*Reason for comment**	*Male*	*Female*	*Male*	*Female*
Mixed infection	2	7 (4)	1 (1)	11 (6)
Persistent infection	2	11 (1)	0	13 (9)
Infection with resistant organism	4 (2)	19 (6)	0	8 (6)
Recurrent infection	1 (1)	NA	0	NA
Infection with unusual organism	1	8 (5)	2 (1)	6 (6)
Resistant or persistent *Proteus* infection	1 (1)	6 (3)	2 (2)	17 (7)
UTI with fever or acute pyelonephritis	2 (2)	4 (1)	0	0
"Sterile" pyuria	1	7 (5)	5 (4)	5 (4)
Total number of patients	10 (5)	53 (22)	10 (8)	49 (29)

NA = not applicable
*For precise definition of reasons see text
Figures in parentheses = number of patients found to have abnormalities

or ureter (6), neuropathic bladder or large residual volume (6), bladder diverticulum (3), pelviureteric junction obstruction (2), pyonephrosis (1), small contracted bladder (1), "interstitial cystitis" (1) and glomerulonephritis (1). Of the remaining 58 patients in whom no abnormalities were detected, 18 underwent only plain abdominal radiography and/or ultrasonography and 1 underwent plain abdominal radiography and isotope renography. If the findings in the 104 adults who underwent IVU or isotope renography are analysed separately, abnormalities were found in 64 (62%).

Discussion

These findings confirm that the indications used for prompting urinary tract investigation yield a high percentage of positive findings. By investigating a very small proportion of the considerable number of patients with proven UTI or apparently "sterile" pyuria a large number of abnormalities were found. It is not possible to give a precise percentage of patients with UTI to whose report the comment was appended because the 12,705 specimens in which infection was diagnosed will have included more than 1 specimen from some patients, and the 652 patients to whose report the comment was appended included some with apparently "sterile" pyuria; the proportion, however, is clearly small. The sample of 233 patients (36% of those identified by the comment) did not differ from the remainder in the distribution of the indications for the comment; it was selected only by the fact that they were referred to the Portsmouth hospitals.

Comparison of the percentage of patients in each referral category in whom abnormalities were found would not be valid in view of the different extent to which individual patients were investigated. Unlike the studies of children identified as bacteriuric in screening programmes and the study by Fowler and Pulaski (1981) of adult women with symptomatic infections, the patients identified in this study were investigated to varying extents by the different specialists to whom they were referred—a practice which is increasingly acceptable at the time of writing. The limited initial investigations, particularly of some children, do not preclude the possibility of more extensive investigation later, should infection recur; 58% of the children investigated at least by IVU or isotope renography showed abnormalities, a percentage considerably higher than that reported in screening studies of bacteriuric children. The percentage of abnormalities detected in adults was also high, 52% overall, and 62% if those who underwent IVU or isotope renography are considered separately. The percentage for women (50%) is considerably higher than the 17% reported by Fowler and Pulaski (1981), in whose study 104 women between the ages of 16 and 72 underwent IVU. It seems, therefore, that the criteria used in this study have considerable predictive value for the presence of urinary tract abnormalities. They will not, of course, identify all patients who have abnormalities—for example, recurrent infection in adult women may be an indication for investigation, but to prompt referral of all such women would be impracticable and unjustified. The use of microbiological criteria such as resistance to antibacterial agents as an indication for investigation must vary from place to place; with the high percentage of sensitivity of urinary pathogens in this area to the commonly used agents, resistance, as defined in this study, is sufficiently unusual to prompt a referral comment.

A laboratory-based study such as this has the advantage that very large numbers of patients are available for analysis; information that would take several years for any one clinician to amass can be obtained fairly quickly. However, the uses to which such findings can be put are various. In some microbiology laboratories the interest and expertise to use the findings in the way described here exist; in others they do not. Clinicians, however, may find the criteria useful even without laboratory guidance. Our purpose in stating on the report the indication for the comment was to stimulate the interest of clinicians in the possible significance of the findings, thus fulfilling an educational function which could have value for the future if laboratory guidance were no longer forthcoming.

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Irrigation and Acute Ureteric Dilatation—as for Ureteroscopy

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Summary—The effects of irrigation with sterile and infected saline after acute ureteric dilatation by graded Teflon dilators were evaluated renographically and histologically in minipigs. The minipig ureter was dilated from its normal calibre of 4 F to 10 F, and 100 ml of sterile or infected saline were then introduced from a height of 60 cm under gravity.

One week after irrigation and dilatation the ipsilateral kidney was either functioning less than 10% or there was an obstructive nephropathy. Histology at 3 months suggested that extravasation of infected irrigating fluid was the most likely cause of ureteric stricture formation.

Previous studies (Boddy *et al.*, 1988) showed that acute ureteric dilatation in minipigs, from 4 to 10 F, caused upper urinary tract obstruction with an obstructive nephropathy for 96 h. This had completely resolved 1 week later. Histology at 3 months showed that the ureter was still dilated but there was no evidence of ischaemic necrosis or stricture formation. However, a stricture rate of 5% has been reported following ureteroscopy (Miller, 1986). This study was designed to investigate the effects of irrigation with sterile and infected saline after acute ureteric dilatation.

Materials and Methods

Four female minipigs weighing 15 kg were used. All procedures were carried out under general anaesthesia, which was induced and maintained by a halothane/oxygen/nitrous oxide mixture administered by a face mask.

Renography

Renal function was assessed by DTPA renography, which was performed by injecting 200 mBq of Technetium-99m DTPA into an ear vein and dynamic images were taken at 10 s/frame for 180 frames using a gamma camera (GE 400 AT). Studies were done pre-operatively and 1, 2, 4, 6 and 12 weeks after surgery; 10 mg of frusemide were injected intravenously after 100 frames if there had been incomplete washout of isotope. Following deconvolutional analysis, parenchymal transit time index (PTTI), whole kidney transit time index (WTTI), relative renal function and the percentage washout with or without frusemide were calculated.

Operative technique

Ampicillin 250 mg was injected intramuscularly at induction of anaesthesia. The bladder was exposed through a laparotomy incision, opened by an anterior vesicostomy, and the ureteric orifices identified. The terminal 4 cm of one ureter were dilated by graded Teflon dilators (6–10 F) passed sequentially over a flexible guide wire. In 2 minipigs the ureter was then irrigated down the 8 F dilator (without the guide wire in place) with 100 ml of sterile N saline, infused into the ureter under the pressure of gravity from a height of 60 cm. In the other 2 minipigs the ureter was irrigated in an identical manner with 100 ml of N saline infected with 10^5 organisms of *E. coli.* In all 4 minipigs the contralateral ureter was used as a control. Bladder

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

and laparotomy wounds were closed in layers with chromic catgut and the animals allowed to recover.

One minipig from each pair was sacrificed 2 weeks after surgery and the other at 12 weeks. At sacrifice, urine samples were aspirated from the bladder and cultured on blood agar plates at 37°C.

Histology

The lower 6 cm of both ureters from each animal with a piece of bladder wall around the ureteric orifice were dissected out and placed in 10% formal saline. Blocks of the specific areas of interest were then embedded in paraffin, step-sectioned at 5 μ and stained with haematoxylin and eosin. Thus histological sections of ureter were obtained 2 and 12 weeks after irrigation and dilatation, plus sections of 4 undilated ureters as normal histological controls.

Results

Renography

All of the kidneys had normal renal function before operation. The mean PTTI was 79 s ± 10, the WTTI was 146 s ± 12 and the RRF on the side to be dilated and irrigated was 51% ± 2 (mean ± standard error). The upper limit of normal for PTTI is 156 s and for WTTI 170 s.

One week after dilatation and irrigation in 3 minipigs the ipsilateral kidney was functioning less than 10%. In the fourth minipig, following dilatation and infected irrigation the ipsilateral kidney showed an obstructive nephropathy with a PTTI of 148 s and a WTTI of 317 s, and the frusemide response was impaired (<65%).

Two weeks after dilatation and sterile irrigation in 1 minipig the ipsilateral kidney function had recovered to 25%, with a PTTI of 61 s and a WTTI of 124 s. At 4, 6 and 12 weeks the ipsilateral kidney function remained at 25%.

Two weeks after dilatation and infected irrigation in 1 minipig the ipsilateral kidney function had decreased from 10% at 1 week to 0% and remained non-functioning on the scan at 4, 6 and 12 weeks.

All urine samples were sterile.

Histology

The ureter remained dilated 2 weeks after dilatation and sterile irrigation. Epithelial fragments were seen lying in the lumen of an otherwise normal ureter; 2 weeks after dilatation and infected irrigation there was persistent ulceration of the transitional epithelium. Fragments of denuded epithelium were seen lying within the lumen and there was oedema and inflammation of the lamina propria (Fig. 1).

There was some macroscopic atrophy of the ipsilateral kidney 3 months after dilatation and sterile irrigation, but histology of the ureter was normal, with no evidence of ischaemic necrosis or stricture formation. There was ipsilateral hydronephrosis and hydroureter 3 months after dilatation and infected irrigation, with a narrowing at the lower end of the ureter (Fig. 2). The lamina propria was thicker and more densely collagenous than normal (Fig. 3).

Discussion

Boddy *et al.* (1988) showed that a 2.5-fold dilatation of minipig ureters from 4 to 10 F caused gross but transient mucosal ulceration with an upper urinary tract obstruction which had completely resolved at 1 week. They showed no evidence of ischaemic necrosis or stricture formation following acute ureteric dilatation alone. Miller (1986) suggested that the post-operative strictures seen after ureteroscopy may be due to the irrigating fluid extravasating into the layers of the ureteric wall. In the present study, irrigating fluid markedly potentiated the damage caused by acute ureteric dilatation alone. After 1 week the gamma camera renogram

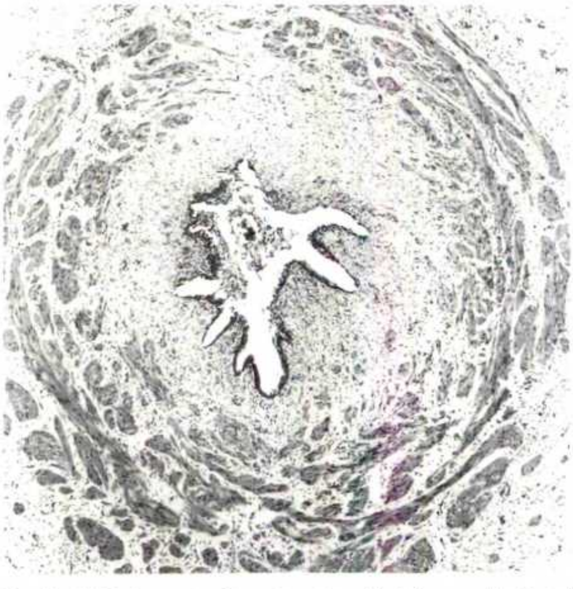

Fig. 1 Minipig ureter 2 weeks after dilatation and infected irrigation. Fragments of denuded epithelium lie within the lumen and there is oedema and inflammation of the lamina propria. (H and E ×32).

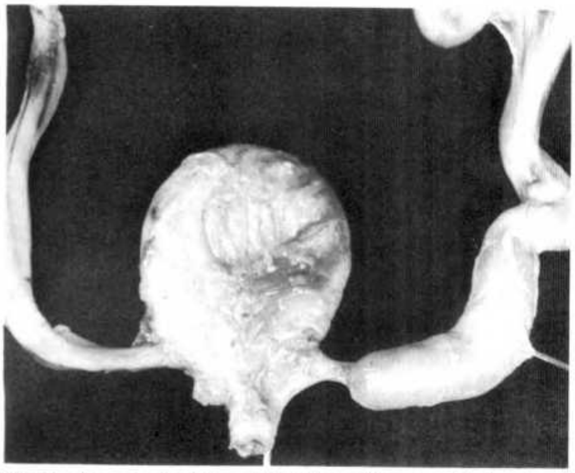

Fig. 2 Autopsy specimen of bladder and lower end of ureters 3 months after dilatation and infected irrigation of the left ureter. There is a stricture at the lower end of the left ureter with dilated ureter above.

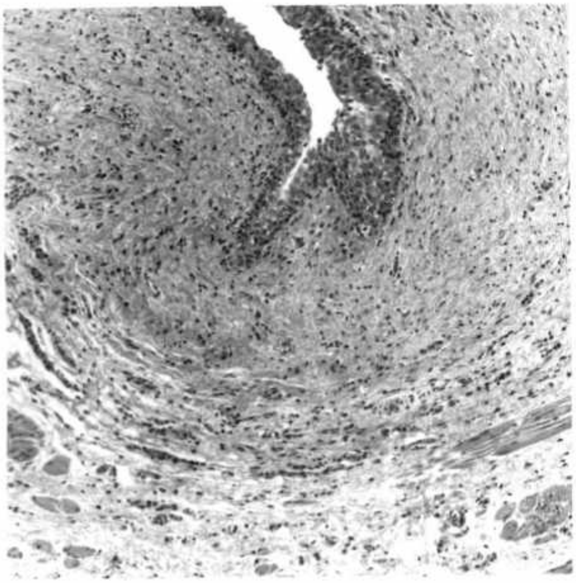

Fig. 3 High power view of minipig ureter 3 months after dilatation and infected irrigation, showing a thicker and more densely collagenous lamina propria which is contributing to the narrowing seen at the lower end of the left ureter in Figure 3. (H and E × 87).

studies showed either a persistent obstructive nephropathy or that the ipsilateral kidney was functioning less than 10%; 2 weeks after acute ureteric dilatation and sterile irrigation the function of the ipsilateral kidney had recovered to 25%. However, 2 weeks after acute ureteric dilatation and infected irrigation the ipsilateral kidney was not functioning at all. Histology 3 months after acute ureteric dilatation and infected irrigation showed a stricture at the lower end of the ureter. Vazquez *et al.* (1987) and Badlani and Smith (1988, unpublished data) advocated jet stream hydrostatic dilatation of the ureter to aid ureteroscopy. The evidence from this study suggests that following acute ureteric dilatation the extravasation of irrigating fluid in the presence of infection is the most likely cause of ureteric stricture formation, and that jet stream hydrostatic dilatation could be hazardous.

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The Severity of Urinary Incontinence in Women
Comparison of Subjective and Objective Tests

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Summary—The subjective assessment of urine loss in 84 incontinent women was quantified by using a 10-cm visual analogue scale. These results were compared with the results of a 2-h pad weighing test. We found no relationship between a patient's subjective impression of the severity of her incontinence and the corresponding objective assessment by a 2-h pad weighing test.

Although visual analogue scores have been used in an attempt to quantify the patient's subjective perception of her urine loss (Parkin and Davies, 1986; Frazer *et al.*, 1987), the accuracy of this perception has not previously been studied. We sought to compare the results of visual analogue scores with the objective assessment of urine loss using a 2-h pad weighing test (Frazer *et al.*, 1987).

Patients and Methods

A total of 110 consecutive women attending a urodynamic clinic were asked to indicate the severity of their incontinence on a 10-cm analogue scale. After a full history and examination each woman underwent a 2-h pad weighing test, with the application of a pre-weighed perineal pad and the performance of a standard exercise regimen in the second hour following a 1-litre fluid load (Sutherst *et al.*, 1986). The increase in pad weight over these 60 min was noted. The patients were also asked to indicate whether urinary loss during the exercise regimen was less than, the same as, or more than their "usual" loss during the same activities performed in more domestic circumstances.

Urodynamic testing included supine and provocative cystometry and urethral pressure measurements at rest and during stress. All definitions and units conformed to standards proposed by the International Continence Society unless specifically noted.

From the 110 patients seen, we compared the visual analogue scores and pad test results of 58 women with genuine stress incontinence (GSI) and 26 patients with detrusor instability (DI). Patients with other diagnoses were excluded from further study. There was no significant difference between the two groups with regard to age or parity.

Results

The Figure shows the results of visual analogue scores plotted against the corresponding result from a 2-h pad test in cases of GSI and DI. Statistical comparison between the two groups was made using Kendall's method of rank correlation for non-parametric data (Kendall, 1970). This gave correlation coefficients (tau values) of 0.177 and 0.258 for DI and GSI respectively. Overall, 67 of the 84 patients (80%) felt that the pad test loss accurately reflected their usual degree of wetness. There was no appreciable difference between the two diagnostic groups in this regard.

Discussion

Our studies revealed no apparent relationship between a patient's subjective impression of the severity of her incontinence and the corresponding objective assessment by a 2-h pad weighing test. In both diagnostic groupings similar degrees of wet-

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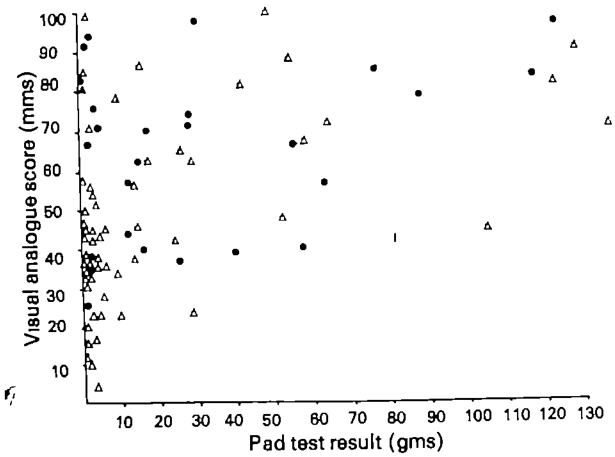

Fig. Visual analogue scores plotted against pad test results in genuine stress incontinence (△) and detrusor instability (●) $\tau = 0.258$ (GSI) and 0.177 (DI).

ness as objectively measured gave rise to large variations in the visual analogue scores. We recently reported our disappointing experience with visual analogue scores as an aid to diagnosis (Frazer *et al.*, 1987).

It is common clinical experience that a stoical individual may cope well with symptoms, incontinence or otherwise, which in a more fastidious patient would prove intolerable. In a few patients, leakage occurs only with activities not included in our exercise regimen (*e.g* aerobics, horse riding, coitus, *etc.*) but, in the main, little reliance can be placed on the accuracy of a patient's own assessment of the magnitude of her urine loss. Since most patients felt the urinary loss during the pad test was a true reflection of their usual degree of wetness, we feel the lack of correlation between the two tests reflects variability in the subjective appreciation of the severity of incontinence rather than deficiencies in the 2-h pad test.

An accurate objective assessment of the degree of urine loss in incontinent women has become increasingly important in clinical practice. Not all women with genuine stress incontinence require or are suitable for operative treatment. Wilson *et al.* (1987) showed that the severity of urinary leakage was a significant prognostic indicator of the success of hospital-based physiotherapy regimens; mild to moderate incontinence was improved more consistently than severe leakage.

Even a careful history concerning the volume of urine lost is likely to be inaccurate. The 2-h pad weighing test overcomes the inadequacies of subjective assessment of incontinence.

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Neurological Defects of the Voiding Reflex Arcs in Chronic Urinary Retention and their Relation to Spina Bifida Occulta

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Summary—A group of 37 patients (24 female and 13 male) with chronic urinary retention and without demonstrable mechanical obstruction had neurophysiological measurements of their lower urinary tracts to detect any neurological abnormality which might relate to the disorder. These consisted of measurements of the electrosensitivity of the dorsal nerve of the penis/clitoris and of the urethra, measurement of the sacral reflex latencies (SRL) from dorsal nerve to urethra and to anus and between urethra and anus and EMG studies of the urethral and anal sphincters. The results suggest that female patients in particular have significant neurogenic defects in the voiding reflex arcs which find their clinical expression in detrusor underactivity with urinary retention. Plain X-rays of the renal tracts (KUB films) were also studied for the presence of spina bifida occulta. The prevalence of this defect was significantly higher than in normal controls, suggesting that in some of these patients the nerve defect might be related to a tethered cord in association with spina bifida occulta.

A large post-voiding residue is evidence of voiding insufficiency. This was classically attributed to mechanical obstruction such as stricture or benign prostatic hypertrophy (BPH) and more recently also as the result of functional obstruction, namely dyssynergia. It has now been shown that residual urine is nearly always the result of a fading away of the detrusor contraction, and rarely a direct effect of either mechanical or functional obstruction *per se* (Abrams and Griffiths, 1979; Griffiths, 1983). Since detrusor function depends on urethral function it is possible that defects in the nerve supply of the urethra and/or defects of the voiding reflex arcs might contribute to such dysfunction. Recent studies have shown that the neurophysiological measurement of the lower urinary tract innervation is more accurate than clinical examination and electromyography (EMG) in describing neurogenic defects (Siroky *et al.*, 1979; Krane and Siroky, 1980; Vereecken *et al.*, 1982; Bilkey *et al.*, 1983). We have studied the nerve supply in a group of patients whose common characteristic was a constant significant post-voiding residue. At the same time we looked at the incidence of spina bifida occulta in these patients in an attempt to correlate in some of them the often unexplained aetiology of the sub-clinical nerve defects with the presence of spina bifida occulta.

Patients and Methods

The group comprised 37 patients (24 females and 13 males). Their mean age was 38 years (±14SD). Chronic retention was defined as the condition where the patient was always able to void but could not totally empty his bladder, leaving a residue which was always >50 ml. This was a constant finding measured at least 3 times, before and after videocystometry and before neurophysiological measurements, through catheterisation. In most patients this was repeated during other tests, or at clinic visits, by ultrasound. Videocystometry and cystourethroscopy excluded mechanical obstruction due, for example, to BPH or strictures, in all

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patients. All patients had a full urological assessment, videocystometry, frequency volume bladder charts and flow rates and other urodynamic tests such as EMG flow rates. IVUs were performed in most cases.

All patients had neurophysiological measurements as described by Galloway *et al.* (1985) and Fidas *et al.* (1985). This briefly consisted of EMG of the urethral and anal sphincters with ring electrodes with the patient relaxed, gripping and coughing; measurement of the sensory thresholds to stimulation of the dorsal nerve of the penis/clitoris and of the urethra and of reflex latencies after electrical stimulation from the dorsal nerve to the urethra and anus and from urethra to anus. KUB films were studied on the 24 cases where they were available and the presence and level of spina bifida occulta assessed. Where spina bifida occulta was present this was classified as a minimal defect in normal laminae, a crossover type defect, where abnormal laminae overlap but fail to unite in the midline, or a larger central defect. In addition, the upper level of opening of the posterior sacral arcs was noted. These findings were compared with those in a control study on a genetically similar population (Fidas *et al.*, 1987).

Results

Table 1 shows the overall number and percentage of abnormal responders for the various neurophysiological measurements. These are compared in the subsequent Figures with the measurements in a group of 59 controls presented previously (Fidas *et al.*, 1985).

Figures 1 and 2 show the distribution of the sensory thresholds in controls and in patients in the dorsal nerve and urethra respectively; 6 patients, 2 males (15%) and 4 females (16%) had an abnormal threshold in the dorsal nerve; 7 males (53%) and 15 females (62%) had abnormal results in the urethra.

Table 1 Number of Patients with Abnormal Results in Neurophysiological Measurements

Test	*No (%) Male*	*Abnormal (%) Female*
Dorsal nerve stimulation.		
sensory threshold	2 (15)	4 (16)
urethral latency	7 (53)	15 (62)
anal latency	3 (23)	17 (70)
Urethral stimulation.		
sensory threshold	1 (7)	17 (70)
anal latency	2 (15)	13 (54)

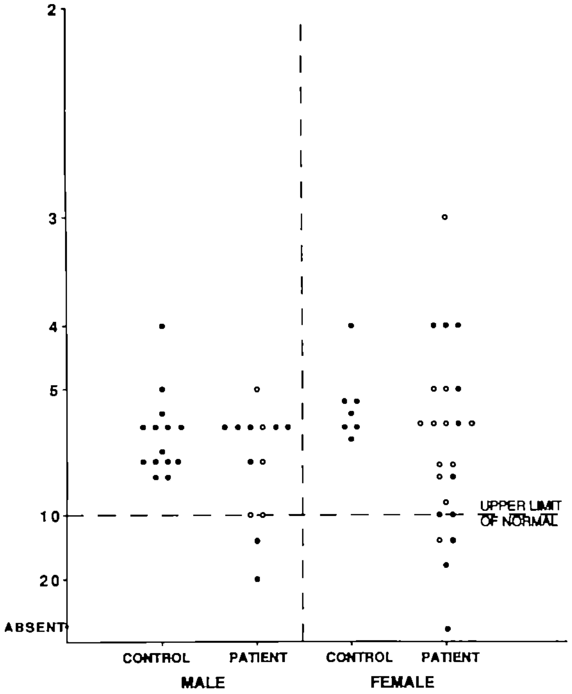

Fig. 1 Sensory threshold in dorsal nerve of penis/clitoris in male and female patients compared with controls.

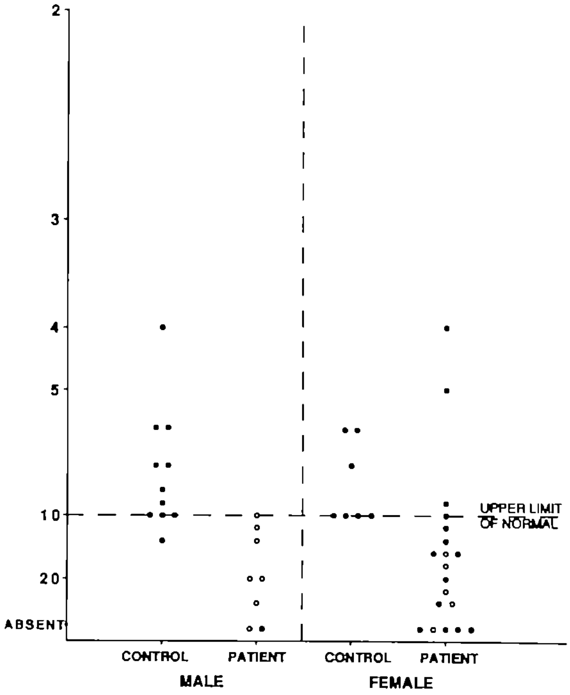

Fig. 2 Sensory threshold in urethra in male and female patients compared with controls

Abnormalities in the dorsal nerve thresholds were not significant when compared with controls but those in the urethra were ($P<0.001$ for males and $P<0.01$ for females).

Figures 3 and 4 show the distribution of latencies after stimulation of the dorsal nerve, recording in the urethral and anal sphincters; 3 males (23%) and 17 females (70%) had an abnormal urethral latency; 1 male (7%) and 17 females (70%) had an abnormal anal latency.

Figure 5 shows that after stimulation of the urethra, 2 males (15%) and 13 females (54%) had an abnormal latency to the anus.

These abnormal latency measurements were not significant in the male patients for any of the reflex arcs studied, but were significant in females for all three pathways; dorsal nerve to urethra ($P<0.01$), dorsal nerve to anus ($P<0.001$) and urethra to anus ($P<0.05$).

When the response was absent the arbitrary value of 99 was given for dorsal nerve to urethra and anus, and 300 for urethra to anus.

No significant relationship was found between any of the neurophysiological measurements and the first desire to void, the maximum functional bladder capacity (Kendall rank correlation) or the maximum voiding pressure (Wilcoxon rank sum

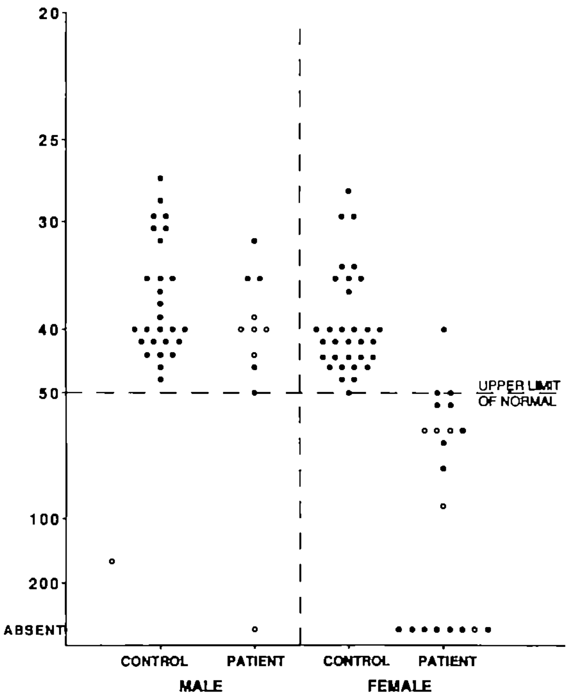

Fig. 4 Sacral reflex latency to anus following stimulation of dorsal nerve in male and female patients compared with controls.

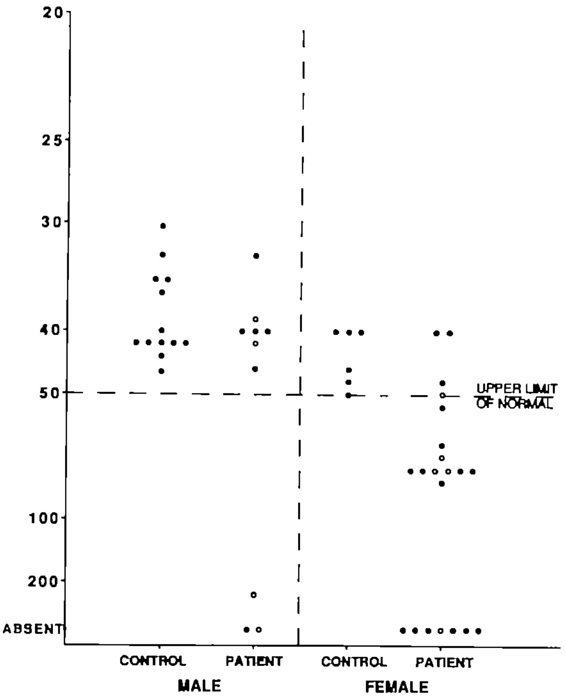

Fig. 3 Sacral reflex latency to urethra following stimulation of dorsal nerve in male and female patients compared with controls

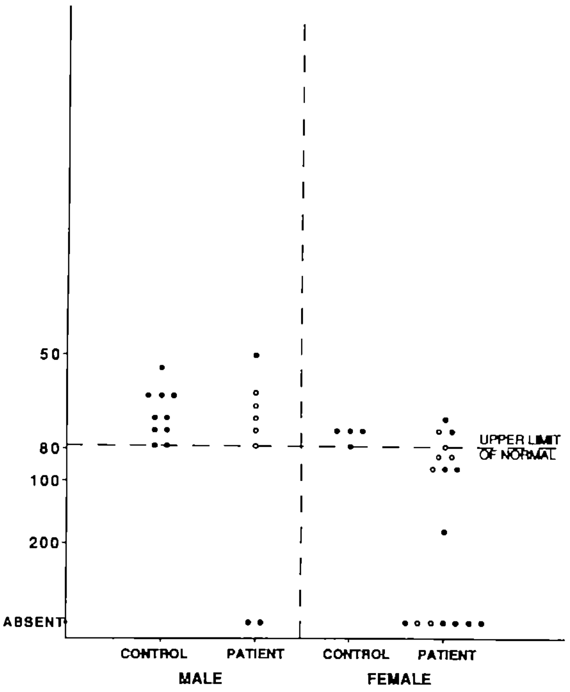

Fig. 5 Sacral reflex latency to anus following stimulation in urethra in male and female patients compared with controls.

test). Only 4 patients had completely normal neurophysiological responses.

On urodynamic assessment the only abnormality in 5 patients was incomplete emptying of the bladder. Detrusor pressure during voiding was invariably low, with only 1 patient achieving 80 cm of water (flow rate 25 ml/s). In 12 patients (1 male and 11 females) the flow rate was >20 ml/s; in the remainder, 92% of males and 54% of females ($P<0.05$), it was abnormally low with a mean of 9.4 ml/s. Videocystometry showed that 10 patients had dyssynergia which was characterised by increased EMG activity during voiding or by an obvious lack of opening of the bladder neck during the voiding phase. The maximum voiding pressure in these patients was >70 cm of water and this was due to abdominal straining; 3 patients had a non-contractile bladder and voided by pure abdominal straining.

The EMG was classified as normal, fair or poor (Fidas *et al.*, 1985). It was normal in 13 patients; in the other 22 abnormal cases 18 were poor and 4 fair. In 2 patients the EMG was not recorded.

KUB films were available on 24 of the 37 patients, 11 males and 13 females; 10 of these (5 males and 4 females) had spina bifida occulta (Table 2). This gave a prevalence of 45% in males and 30% in females, which was greater than the control figures of 30% and 17% respectively but not statistically significant. The posterior sacral arcs opened at a higher level in both male and female patients than in the controls (Table 3); 54% of male patients compared with 22% of controls had arcs open from SV3 or above ($P<0.05$). In females the figures were 46 and 15% respectively ($P<0.01$).

Table 4 shows the 11 patients with a known cause of possible neurogenic damage which might explain their urinary problems. No cause was found, on the basis of the clinical history, in the remainder. Radiology was available on 7 of the patients in the latter group. When the figures for spina bifida occulta are corrected to exclude those patients with neurological damage, the prevalence in the remainder rises to 55% in males but remains at 33% in females.

Table 2 Prevalence and Patterns of Spina Bifida Occulta in Patients and Controls

	Male		Female	
	Patients (%)	*Controls (%)*	*Patients (%)*	*Controls (%)*
Spina bifida	5 (45)	402 (30)	4 (30)	229 (17)
Min defect	1 (9)	123 (9)	1 (8)	66 (5)
Crossover	1 (9)	127 (9)	3 (23)	105 (8)
Symmetric	3 (27)	99 (7)	0 (0)	31 (2)
Asymmetric	3 (27)	138 (10)	0 (0)	67 (5)
Total No.	11	1359	13	1348

Patterns of defect are as described by Fidas *et al* (1987). Some of the male patients had spina bifida defects at more than one level

Table 3 Upper Levels of Opening of Posterior Sacral Arcs in Patients and Controls

	Male		Female	
	Patients (%)	*Controls (%)*	*Patients (%)*	*Controls (%)*
SV1	4 (36)	89 (6)	0 (0)	51 (4)
SV2	1 (9)	31 (2)	3 (23)	15 (2)
SV3	1 (9)	186 (14)	3 (23)	143 (10)
SV4	2 (18)	504 (37)	5 (39)	516 (39)
SV5	3 (27)	549 (41)	2 (15)	623 (46)
Total No	11	1359	13	1348

The tendency to a higher level of arc opening in the patients is significant ($P<0.05$ for males, $P<0.01$ for females)

Table 4 Patients with a Known Cause of Possible Neurological Damage from the Clinical History

Clinical history	*Number*
Hysterectomy	4
Chondrosarcoma	1
Laminectomy (TB)	1
Cervical spine trauma	1
Lumbar spine trauma	1
Myelomeningocele	1
Multiple sclerosis	1
Thalidomide	1

Discussion

This study has shown both urodynamic and neurophysiological abnormalities in patients with residual urine. The urodynamic findings suggest that in those patients with a chronic residue, even in those with obstruction such as detrusor sphincter dyssynergia, the detrusor pressure was low compared with normal values (Abrams *et al.*, 1983). In this department we do not routinely carry out videocystometry on patients with mechanical obstruction such as BPH but without residue, so we do not have our own normal values for comparison. Griffiths (1983) and Abrams and Griffiths (1979) showed a similar pattern of low detrusor pressure in patients with chronic residue.

The power and duration of detrusor contraction depends on the integrity of the urethra and the micturition reflex arcs connecting and co-ordinating urethra and bladder. If these reflexes are damaged, as in our patients, the system functions in an imperfect and unco-ordinated way. One of the results might be an inefficient voiding act with residual urine.

It is of note that in this group of patients with chronic residue but no mechanical obstruction, while low flow rates in male patients were the rule rather than the exception, the significant abnormalities in the voiding reflex arcs were found in female patients. The sensory thresholds in the urethra were, however, significantly abnormal in both males and females. The fact that similar nerve defects are found in patients with differing presenting complaints, such as enuresis or stress incontinence, is not readily explained. Defects in different levels of the reflex arc or inappropriate interconnections within the arc will give the same neurophysiological abnormality on measurement but may produce a different clinical picture. Patients cannot be divided into strict clinical groups because most have several urodynamic abnormalities but in differing degree and with only one or two sufficiently troublesome to be taken into consideration. Symptomatology may also be in part attributable to local factors, for example scar tissue in patients with stress incontinence.

The prevalence of spina bifida occulta was greater in the patient group and there was also a tendency to a higher level of opening of the posterior sacral arcs. This was equally true for males and females, taking into account the increased prevalence of spina bifida occulta defects in the normal male population. These bony stigmata of abnormal tail bud development may be related to the neurogenic bladder demonstrated on neurophysiological measurements. Spina bifida occulta can be associated with tethering of the cord (James and Lassman, 1981) and several authors (Hellstrom *et al.*, 1986; Kondo *et al.*, 1986) have shown that this may be associated with detrusor underactivity. Peripheral neurone damage will produce an underactive detrusor which will be responsible for incomplete bladder emptying. Since bladder function depends on urethral function it is possible that damage to urethral innervation, which we have demonstrated in this study, is responsible for the detrusor underactivity. It is not possible to comment on any coexistent decentralisation of the detrusor secondary to a tethered cord because this is not susceptible to direct measurement.

It was concluded that incomplete emptying of the bladder resulting from an underactive detrusor seems to have a significant neurogenic component in both sexes which in some patients may be in part due to a tethered cord associated with spina bifida occulta.

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Assessment of the Results of Stamey Bladder Neck Suspension

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Summary—A total of 48 patients with genuine stress incontinence underwent endoscopic bladder neck suspension; 36 patients (75%) were completely cured of their incontinence but 12 (25%) suffered recurrent leakage. In 2 cases this was due to infection and erosion of the vaginal sutures; in 4 cases failure was ascribed to a small capacity bladder and "pipe-stem" urethra. In the remaining 6 unsuccessful cases the Stamey sutures had cut through flimsy endopelvic fascia.

It was concluded that endoscopic bladder neck suspension has advantages over colposuspension in terms of reduced dissection and hospital stay, but its success rate is lower than originally reported. Failures due to suture infection and buttress displacement may be avoided by not using Dacron and, instead, by picking up vaginal subdermis with nylon sutures—the same tissue used to provide support in a Burch colposuspension.

Since its description by Stamey (1973), endoscopic bladder neck suspension has gradually become accepted as a means of treating genuine stress urinary incontinence. The operation has advantages over the more widely used Burch colposuspension in its technical simplicity, post-operative comfort for the patient and reduced hospital stay. However, whether the Stamey operation with its limited dissection achieves long-term cure rates equal to those of open retropubic procedures is still controversial. Stamey reported a success rate of 91% in 1980, but subsequent reports (Table 1) have suggested that a smaller proportion of patients than this are cured by the procedure.

In order to assess the efficacy of endoscopic bladder neck suspension and to determine in which patients the operation is most likely to be effective, the results achieved in a personal series of 48 patients have been analysed: in those patients who remained incontinent after surgery, the reasons for failure are considered.

Table 1 Previous Reports of Success Rates for Stamey Operation

	No of patients	*Length of follow-up (months)*	*Success rate (%)*
Stamey (1980)	203	6	91
Fowler (1986)	40	1–39	86
Diaz *et al* (1984)	31	2–6	64
Gaum *et al.* (1984)	60	6	82
Vordemark *et al.* (1979)	20	2–23	75
Ashken *et al* (1984)	60	10–36	84
Fleischer *et al.* (1984)	48	0 5–41	63
Huland and Butcher (1984)	66	20–90	71 2
Mundy (1983)	25	12	76
Spencer *et al* (1987)	41	21–118	57

Patients and Methods

Between 1985 and 1988, 48 patients presenting with genuine stress incontinence were operated upon by one surgeon (RSK). Their mean age was 57 years (range 29–90). The nature of the urinary leakage and the number of patients who had undergone one or more previous operations for stress incontinence are shown in Tables 2 and 3. All patients underwent pre-operative urodynamic testing with simultaneous X-ray screening, to confirm the diagnosis of genuine stress leakage and to assess bladder filling and voiding characteristics (Table 4).

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Table 2 Nature of Urinary Leakage

Presenting symptoms	*No. of patients*
Leakage on exercise	10
Leakage on coughing/sneezing or movement	30
Total incontinence	8
Total	48

Table 3 Previous Operations for Stress Incontinence

No of operations	*No. of patients*
0	25
1	10
2	5
3	4
4	2
5	2
Total	48

Table 4 Urodynamic Test Results

Urodynamic findings	*No of patients*
Stress incontinence and stable bladder	39
Stress incontinence and mild instability	9
Total	48

The operative procedure was similar to that described by Stamey (1973). Prophylactic antibiotics were administered with the premedication. The patient was anaesthetised without the use of an endotracheal tube and a caudal block performed with 0.5% Marcain. After an initial cystoscopy, a Foley catheter was inserted into the bladder and the length of the urethra determined. Instead of a single transverse incision, 2 separate vertical vaginal incisions were made on each side of the junction between the urethra and bladder neck. These were enlarged to accept the tip of the fifth digit. The Stamey needle was then passed from small suprapubic incisions twice on each side and correct siting was checked endoscopically. A number 2 nylon suture was threaded over a 1-cm length of 6-mm Dacron to create a loop on each side. The abdominal sutures were also tied over 1-cm Dacron segments initially, but later in the series this was changed to 1-cm segments of silicone tubing. At the end of the operation a suprapubic catheter and a vaginal pack were inserted.

The suprapubic catheter was clamped between the third and fifth post-operative days and removed when voiding was re-established and the residual urinary volume fell below 100 ml.

The duration of follow-up varied from a maximum of 3 years to a minimum of 6 months and the operation was regarded as a success if patients were completely free of stress urinary leakage on examination with a full bladder. In the event of any post-operative stress incontinence, the operation was regarded as unsuccessful and further urodynamic studies were arranged. If this investigation revealed persistent bladder base descent and urethral insufficiency, a second procedure—usually a Burch colposuspension—was performed and the reasons for the failure of the Stamey operation appraised.

Results

Thirty-six patients were cured of stress urinary incontinence, the overall success rate for endoscopic bladder neck suspension being 75%. All patients were able to void satisfactorily on clamping the catheter and no patient was sent home with the suprapubic tube in place. The mean length of hospital stay was 6.5 days.

Complications occurred in 6 patients (12.5%). In 3 cases this consisted of persistent pain in the region of one of the two abdominal wounds, and in 1 case this necessitated removal of the suture, after which the patient remained continent. In 3 patients infection developed in the vaginal wounds; these patients complained of a vaginal discharge and examination revealed areas of granulation tissue. In 2 of these cases the removal of sutures from both sides was required with return of incontinence, while in the remaining case a single suture was removed and continence was maintained.

Twelve patients (25%) complained of persistent or recurrent urinary incontinence during the follow-up period and they underwent repeat urodynamics. In 2 cases this was the result of removal of the sutures because of the vaginal infection mentioned above. In 4 patients failure was due to a combination of a small capacity, unstable bladder and a fibrotic "pipe-stem" urethra which continued to leak in spite of adequate repositioning. In the remaining 6 unsuccessful cases bladder descent recurred together with stress urinary leakage. In 5 of these patients this failure was evident at first follow-up, but in 1 case failure occurred at 12 months, when the patient felt "something snap" during a bout of coughing. Each of these patients subsequently underwent a Burch-type colposuspension, when the Stamey sutures were noted to be lax and the periurethral Dacron segments were seen to have cut through the flimsy pubocervical fascia. In every case a Burch colposuspension was curative, although 1 patient still has troublesome frequency.

Discussion

The results achieved in this series demonstrate that although the Stamey procedure is easy to perform and has a low morbidity rate, its success in curing stress urinary leakage is not as high as originally reported (Stamey, 1980). Failure to achieve a clinical cure of stress leakage is disheartening for patient and surgeon alike. In 4 of our patients in whom failure was ascribed to a small capacity bladder and/or a "pipe-stem" fibrotic urethra, it seems unlikely that a Burch colposuspension or similar procedure would have been curative. In Stamey's series (1980), nearly 50% of the failures were in patients with "total urinary incontinence", a group which is difficult to evaluate urodynamically. In these patients, although it could be argued that there seems little to be lost by attempting a Stamey operation, a pubo-urethral sling procedure or implantation of an artificial sphincter is more likely to be curative.

The 8 patients in whom the operation was judged to have failed because of infection (n = 2) or cutting through of the peri-urethral Dacron buttresses (n = 6) highlight two inherent weaknesses in the Stamey procedure. The placement of Dacron segments superficially beneath the skin makes them liable to infection, especially in the vagina. Other authors have reported a significant incidence of Dacron buffer associated infection (Table 5). The displacement of the Dacron buttresses, either in the short or longer term, results from the inability of the flimsy pubocervical fascia to withstand the forces acting through them during coughing, sneezing or exercise. For both of these reasons we have recently abandoned the use of Dacron segments in this operation, preferring instead to enlarge the vaginal incisions slightly, to mount the number 2 nylon suture on to a needle and pick up both endopelvic fascia and vaginal dermis—the same tissue used for urethral support in the colposuspension. To date, using this technique in a limited number of patients, we have seen neither wound infection nor suture displacement.

Table 5 Incidence of Suture Infection in Stamey Operations

	No of patients	*Suture infection (%)*
Stamey (1980)	203	0
Fowler (1986)	40	2
Diaz *et al* (1984)	31	10
Gaum *et al* (1984)	60	1 6
Vordemark *et al* (1979)	20	5
Ashken *et al* (1984)	60	0
Fleischer *et al* (1984)	48	16
Huland and Butcher (1984)	66	15
Mundy (1983)	25	16
Spencer *et al* (1987)	41	12

In conclusion, although the Stamey operation has attractions in terms of limited dissection and a shortened stay in hospital, its success rate is not as high as was originally claimed. It is especially prone to fail in patients with total urinary incontinence, in whom other procedures may be more effective. Some of the failures of this operation are due to infection or displacement of the Dacron segments and we suggest that these be discarded and that the vaginal dermis and pubocervical fascia be picked up by the nylon sutures.

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Lack of Relationship of Conus Reflexes to Bladder Function after Spinal Cord Injury

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Summary—A series of 20 patients with acute complete suprasacral cord lesions underwent serial urodynamic assessment of vesicourethral function and serial measurement of sacral reflex latency times (SRL) and reflex threshold throughout a follow-up period of 42 to 83 weeks (mean 50).

No correlation was found between any pattern of SRL latencies or reflex thresholds and subsequent bladder behaviour. The reproducibility of sacral reflex latencies was found to be poor (mean variation of serial measurements from initial reading 21%) and could not be explained on the basis of "dynamic" neurological recovery. Studies using the bladder as a stimulus site were unreliable. The value of SRL studies in detecting subtle neurophysiological changes is discussed.

Following a traumatic injury to the spinal cord we expect to observe a pattern of bladder activity which depends on the level of the neurological lesion (Head and Riddoch, 1917). During the phase of "spinal shock" we repeatedly examine the patient for evidence of return of both the anal skin reflex and the glans bulbar reflex, or the "conus reflexes". When they are present we predict with some confidence that reflex bladder activity will subsequently recover.

This observation implies the existence of a "sacral micturition reflex", analogous to the clinical conus reflexes, recovery of which is required in order for reflex bladder activity to occur. Such a simplified concept, however, fails to explain certain anomalies. Firstly, the speed of bladder recovery varies greatly from patient to patient, even when conus activity is the same (Arnold *et al.*, 1984). The bladders of some patients with apparently normal conus reflexes never regain reflex activity. Secondly, in patients with similar patterns of neurological recovery and, in particular, similar conus reflexes, there are enormously varying degrees of detrusor–sphincter co-ordination, resulting on the one hand in an efficiently emptying reflex bladder and, on the other, a high pressure dyssynergic voiding system which is hazardous to upper tract function (Blaivas *et al.*, 1981; Siroky and Krane, 1982; Wyndaele, 1985).

The aim of this project has been to examine the relationship between sacral afferent and reflex activity, when assessed by neurophysiological techniques, and the patterns of bladder and sphincter function which are seen following an acute spinal cord injury.

Patients and Methods

Twenty patients with acute complete suprasacral cord lesions, admitted over a 12-month period, were studied. They included 18 males and 2 females (age range 15–45 years, median 45). There were 9 cervical lesions and 11 injuries to the thoracic cord. Although all had complete motor and sensory loss at the time of admission, 3 patients with cervical fractures subsequently developed a degree of sensory sparing within the sacral root distribution.

Recovery phase

Immediately upon admission to the Spinal Injuries Unit, and subsequently during the recovery period (the period of immobilisation which usually lasts for approximately 6 to 10 weeks), patients were

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regularly examined for evidence of motor or sensory recovery below the lesion. Simple 2-channel cystometry was performed every other week, to detect the approximate time when bladder contractions first occurred in response to bladder filling. Sacral reflex latency times and reflex thresholds (see below) were performed at least twice during this initial period.

Established phase

Once the bony lesion was stable and the patient was mobilised, video-urodynamic studies (see below) were performed for a detailed assessment of vesicourethral function and SRL studies were repeated, both at least twice during a follow-up period of 42 to 83 weeks (mean 50).

Sacral reflex latency studies

This technique is well documented (Siroky and Krane, 1982; Galloway *et al.*, 1985). A number of theoretical neural pathways associated with micturition were assessed in this study. Electrical stimuli were applied, independently and in turn, to the dorsal nerve of the penis (bipolar surface electrode), the proximal urethra and the bladder mucosa (separate bipolar ring electrodes mounted on the shaft and tip of a 14F Foley catheter).

Electromyographic responses were recorded from either a concentric monopolar needle electrode (Disa 13L50), inserted into the superficial part of the external anal sphincter in women and into the bulbocavernosus muscle in men, or the urethral ring electrode lying within the distal urethral sphincter mechanism which was reconnected to an input channel on the EMG pre-amplifier. Reflex latency times and reflex thresholds were measured for each combination of stimulation and recording site.

The equipment used for all neurophysiological tests was the Dantec Neuromatic 2000M (band width 20 Hz–2 kHz); 200 µs pulses were delivered at a rate of 3 Hz. Measurements were made from averaged responses, from trains of up to 100 stimuli applied at supramaximal level (3 × threshold level).

Videourodynamics

Combined filling and voiding cystometrograms, with simultaneous radiological screening and video recording, were used to assess vesicourethral function in detail, once the patient could be easily transferred to the X-ray department. Our usual technique for studying neurogenic bladder dysfunction was used (Thomas, 1979).

Vesicourethral function was assessed according to the recommendations of the International Continence Society. Bladders were recorded as being either hyper-reflexic, hypocompliant or acontractile in behaviour. Detrusor sphincter dyssynergia (DSD) was assessed radiologically and in relation to changes in bladder pressure and recorded as being either absent, early (lasting less than 30 s, prolonged (showing repetitive contractions of the sphincter unit in association with detrusor contraction), or terminal (occurring in the terminal phase of voiding, *i.e.* preventing complete bladder emptying). Bladder emptying was regarded as efficient when the residual urine was less than 100 ml in the absence of vesicoureteric reflux. Thus emptying was recorded as being good, bad or absent. When emptying was bad, this was assessed as being due to either DSD or poorly sustained detrusor contractions or both.

Results

Figure 1 shows how, in the majority of patients, clinically detectable conus reflexes reappeared within 8 days of the injury and 9 of these were recorded in the first 24 h. It is possible that these reflexes had never disappeared. Only 1 patient had electrically detectable reflexes before they were present clinically (35 weeks). All except 3 patients subsequently developed normal somatic reflexes although, even in these 3, the conus reflexes had returned (24 h, 35 days and 80 days).

Bladder function

The time taken for detrusor activity to recur varied from 4 to 37 weeks and showed no relationship with the level of the neurological lesion (Fig. 2). All but 3 patients eventually developed hyper-reflexic bladder activity. Nine patients had efficiently emptying hyper-reflexic bladders and 6 had hyper-reflexia

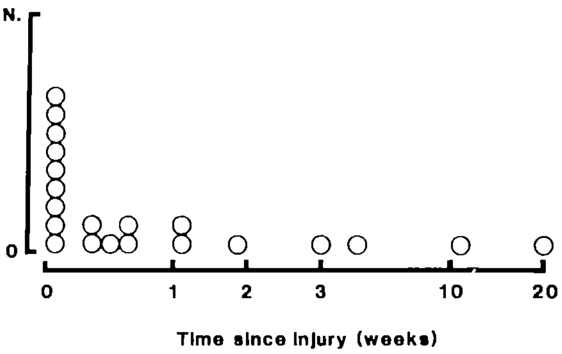

Fig. 1 Time elapsed since injury before clinically detactable conus reflexes appeared

with poor emptying due to DSD; 3 had poor emptying due to poorly sustained detrusor contractions and 3 had persistently acontractile bladders after a minimum of 15 months from injury.

Sacral reflex latencies and thresholds

When recordable, the latency values were normal in 84 to 93% of recordings (Table 1). Normal values had been previously established for our technique from a group of 20 healthy volunteers and corresponded to all previously reported normal ranges. Reflexes were unrecordable in 5 to 16% of studies. Only 2 recordings in the entire series had a prolonged latency time. Thus there was little evidence from these data of any continuing sacral neuropathy once conus reflex activity had recurred. Reflexes resulting from stimulation of the bladder fundus were found to be unreliable.

An attempt was made to correlate neurophysiological findings with urodynamic findings. Both the eventual outcome for bladder and sphincter behaviour and the changes which had occurred during the follow-up period were correlated with the patient's age, neurological level of the injury, the time of appearance of clinical conus lesions and subsequent patterns of normal, abnormal or absent sacral reflex latencies and threshold recordings. No correlation was seen between any of these sets of parameters, other than to reaffirm that the appearance of clinical conus reflexes predicts bladder recovery reliably (85% of patients).

Although most latency values were within normal limits, serial recordings were found to vary from initial recordings, at the time of admission, by between 18 and 25% (Table 2). There was no temporal relationship of these latency values to the time elapsed since injury and thus these figures reflect the poor reproducibility of these tests and not any dynamic neurological recovery occurring over this period. The mean variations for reflex threshold were 88% for the dorsal nerve threshold and 97% for the posterior urethral threshold.

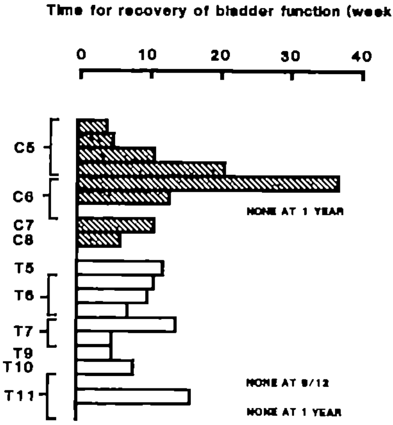

Fig. 2 Time taken in each patient for detrusor activity to recur. No relationship is seen to level of injury.

Table 1 Distribution of Latency Times Recorded for Each of the Sacral Reflexes Studied

	Normal (%)	*Absent (%)*	*Abnormal (%)*
DNP–B/C	93	5	2
DNP–US	84	16	
PU–B/C	84	16	

Table 2 Reproducibility of Serially Recorded Sacral Reflexes. The Mean Variation of Subsequent Recordings, in Relation to Initial Recordings on Admission, was Calculated for each of the Reflexes Studied and for Reflex Threshold Values

		%
Latencies	DP–BC	18
	DP–US	19
	PU–BC	25
Thresholds	DP	88
	PU	97

Discussion

Sacral reflex latency studies have been enthusiastically applied by urologists as an "accurate and sensitive" means of detecting occult sacral neuropathy (Siroky *et al.*, 1979; Galloway *et al.*, 1985; Fidas *et al.*, 1987 a and b). However, doubt has been cast on their value in specific clinical situations (Paquin *et al.*, 1985; Benvenuti *et al.*, 1987; Desai *et al.*, 1988). Since the incidence of abnormal reflexes in the normal population is unknown (no large study of normal controls has been reported), the significance of these abnormal responses is uncertain. It could represent, on the one hand, a variant of normal or, on the other, a localised anatomical or physiological disruption of reflex pathways within the sacral cord or abnormal modulation of sacral reflex activity from a supraspinal level. Even in spinal cord injured patients with apparently complete lesions, supraspinal influence on segmental reflex activity has been shown to occur (Cioni *et al.*, 1985). Such modulation may be of fundamental importance in determining patterns of reflex activity, but has not been investigated.

This study of 20 patients with acute spinal cord injuries has demonstrated that the tests are of little value in spinal cord injury since they reveal no more about the predicted recovery of either somatic or bladder reflex activity than does a simple clinical examination of the conus reflexes.

SRL studies almost certainly test the integrity of myelinated neural pathways and a common "pool" of neurones at cord level. Fowler (personal communication) pointed out that any reflex from the perineum to the spinal cord, and back, with a latency of less than 100 ms cannot possibly be conducted via autonomic nerves, which are all slow conducting fibres. Furthermore, the lack of reproducibility within the group who were studied serially, albeit recovering from neurological injury, raises doubt as to value of SRL tests in detecting subtle neurophysiological changes.

No correlation has yet been confirmed between any currently measurable neurophysiological parameter and patterns of bladder and sphincter behaviour following spinal cord injury. Mundy (1987) suggested that the recovery of bladder function is dependent not on the recovery of existing reflex pathways but on the establishment of new pathways through existing (but unused) synapses, possibly left vacant after loss of the long routed micturition reflexes (Torrens, 1985). Inevitably this would result in variable complexity of these newly established pathways and some may never develop at all. This could account for the various patterns of detrusor sphincter co-ordination and also explain why a number of patients with suprasacral lesions never regain bladder activity. Although there is no evidence for this hypothesis, in this light it would seem obvious that the integrity of a simple somatic reflex, such as is tested clinically with a conus reflex or neurophysiologically by SRL, has little relevance to the sort of complex pathways that may become established to permit reflex bladder action.

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Poor Compliance Early in Filling in the Neuropathic Bladder

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Summary—A total of 30 patients with known neuropathy, mostly spina bifida, developed poor bladder compliance early in filling demonstrated urodynamically; 20 had bilateral hydronephrosis at the time of presentation and 5 also had severely impaired renal function. After appropriate treatment all of those with normal upper tracts or with bilateral hydronephrosis but normal renal function stabilised or improved. However, all 5 with severely impaired renal function progressed to end-stage renal failure. Poor compliance early in filling is an absolute indication for surgical intervention.

It has been known for many years that neuropathic bladders, especially those which are congenital in origin, may rapidly compromise the upper tracts, often after years of normal renal function. More recently, precise urodynamic assessment, categorisation and treatment of children with neuropathic vesicourethral dysfunction have been developed (Mundy *et al.*, 1982; Rickwood *et al.*, 1982). Such neuropathic bladders may be contractile, acontractile or, most commonly, of an intermediate type similar to those seen in traumatic cord lesions at the thoraco-lumbar region. It is in this intermediate group that poor compliance early in filling is likely to develop. Obstruction at the rhabdosphincter is the rule and in only 1 patient have we seen no outflow resistance. It seems likely that this permanent outflow obstruction produces the thickened fibrous sacculated bladder with poor compliance, and the fact that it tends to occur in the teenage group is probably due to the duration of the obstruction, which becomes worse with time.

Patients and Methods

Over the past 5 years 90 patients (66 with spina bifida) with known non-traumatic neuropathy affecting their bladders have been referred for urodynamic investigation and treatment. Thirty of these, the great majority with spina bifida (Table 1), exhibited poor compliance early in filling, with pressures rising to at least 40 cm of water (Fig. 1). More patients with acquired neuropathy would probably be seen were they not treated earlier, before poor compliance develops.

Of the 30 patients, 24 were of the intermediate type with static obstruction at the rhabdosphincter, but 6 were "acontractile" spina bifida patients who had already undergone sphincterotomy and implantation of an artificial sphincter; they had developed poor compliance between 6 months and 5 years after surgery and presented with recurrent incontinence (Fig. 2). Because the paediatric spina bifida patients in South Wales are looked after by one consultant in the Spina Bifida Unit and referred only if urological problems arise, most of the patients in this series had developed upper tract problems at the time of referral and the majority were male teenagers (Fig. 3). In the congenital group with spina bifida, apart from those who had been classified as acontractile and had undergone sphincterotomy and implantation of an artificial sphincter, all but 2 had a degree of hydronephrosis

Table 1 Poor Compliance in the Neuropathic Bladder Aetiology

Spina bifida	26
Acquired neuropathy	3
Following abdominoperineal resection	1

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

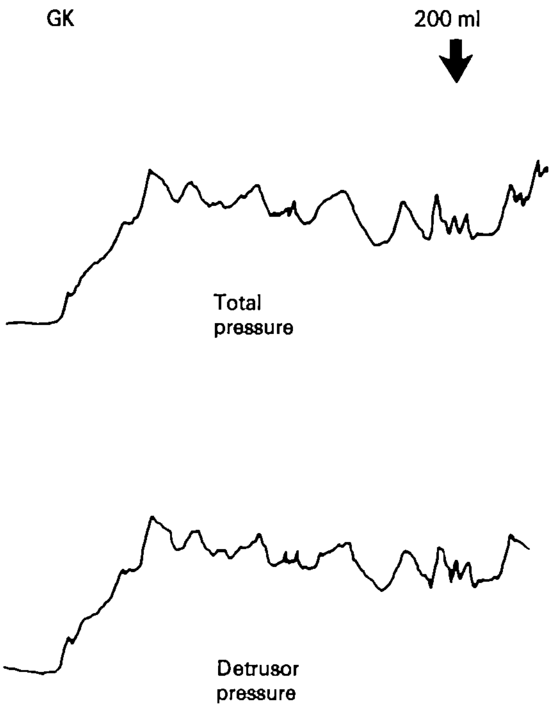

Fig. 1 Poor compliance early in filling

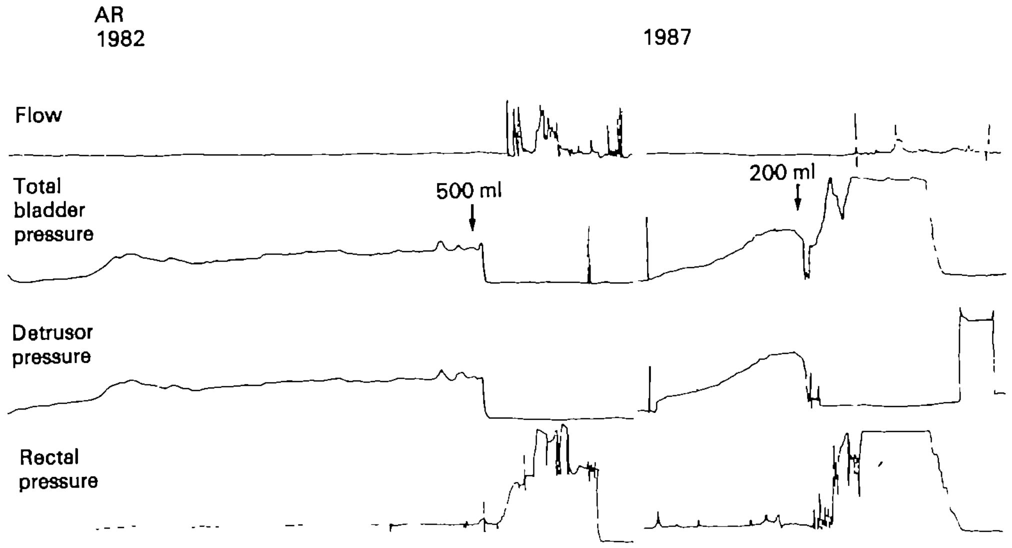

Fig. 2 Urodynamics 1 year and 5 years after insertion of an artificial sphincter into a patient with an "acontractile bladder".

(Fig. 4) or severely impaired renal function or both (Table 2). Although most patients were incontinent, 3 kept dry with intermittent self-catheterisation but still developed hydronephrosis.

All patients were treated surgically; 13 were wheelchair-bound and all but 2 of these were treated by sphincterotomy alone to achieve complete emptying and a low pressure system. Two intelligent motivated patients underwent cystoplasty and voided by intermittent self-catheterisation.

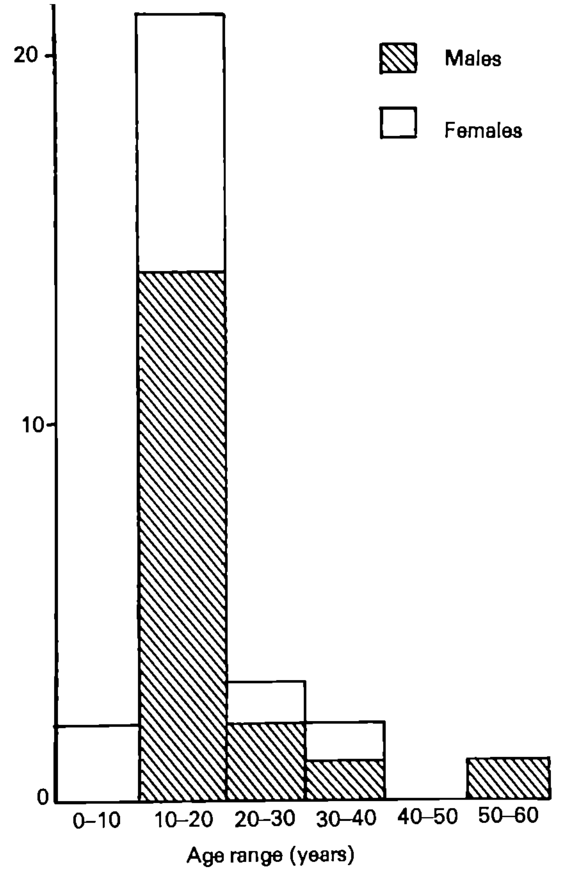

Fig. 3 Age range and sex distribution of patients with poor compliance.

All ambulatory patients (17) underwent major reconstruction. The "acontractile" group with sphincters had a clam ileocystoplasty (6) and the remainder underwent substitution cystoplasty using the ileocolic segment; 11 patients in this group had artificial sphincters and 6 self-catheterise; 3 patients with caecocystoplasties required subsequent detubularisation to eliminate nocturnal enuresis.

Results

All patients who had normal upper tracts at the time of presentation or hydronephrosis but normal serum creatinine either stabilised or improved after treatment. The 5 patients with severely impaired renal function (creatinine >250 mmol/l) deteriorated to end-stage renal failure and have undergone or await transplantation (Table 3). It is not clear why stabilisation is not achievable in this latter group, but it is probably due to a combination of adynamic ureters, intrinsic renal disease, difficulty in eradicating urinary tract infection, especially *Pseudomonas*, and in some instances hypertension which is difficult to control. Nevertheless, it is better to create a suitable reservoir in preparation for a donated organ while some renal function remains, since healing is better and the problems of a "dry" mucous secreting reconstruction are avoided.

Table 2 Upper Tract Status at Presentation

Normal	10
Hydronephrosis but normal creatinine	15
Severely impaired renal function (creatinine >250 mmol/l)	5

Table 3 Results of Treatment in Terms of Renal Function

Normal upper tracts pre-op. → normal post-op.		10
Bilateral hydronephrosis pre-op	↗ improved	13
	↘ stable	2
Severely impaired renal function pre-op. → end-stage renal failure		5

Discussion

The combination of amniocentesis and a selective regime to ensure the survival of only the less severely handicapped has reduced the incidence of patients with overwhelming physical and intellectual disability. Nevertheless, there is a large population (particularly in South Wales) of disabled children and young adults who have survived neurosurgical and orthopaedic problems (surgery) and whose remaining problems are urinary incontinence or renal impairment or both.

About 14% of patients with spina bifida have secondary upper tract complications at birth. It has been suggested by Cass (1976) that the subsequent risk is greatest in the first 5 years of life, but this has not been our experience, where teenagers with poor compliance early in filling, residual urine and recurrent infection are certain to suffer renal impairment. The critical bladder pressure seems to be about 20 cm of water. Permanent pressures above this level cause upper tract damage and most of our patients who experienced rapid deterioration had pressures of at least 40 cm of water. Hyperreflexia alone is unlikely to damage the upper tracts but if it is associated with reflux, which is found in

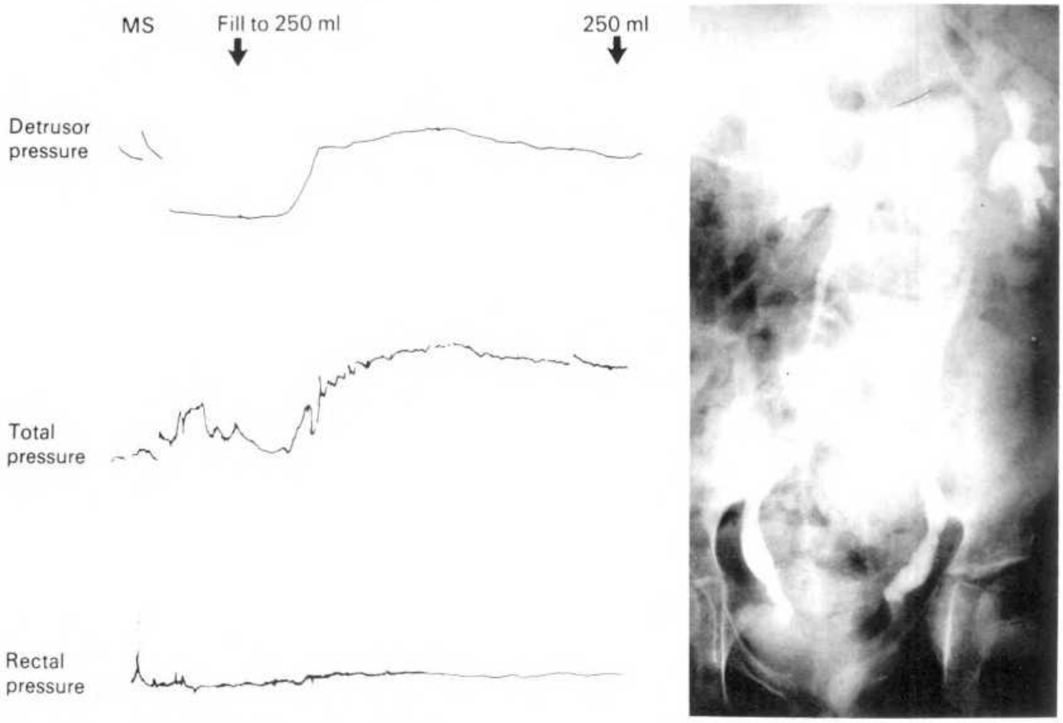

Fig. 4 Poor compliance early in filling with early hydronephrosis.

20% of neonates (Light and Van Blerk, 1977), renal impairment is again almost inevitable.

The other potential risk factor to the teenage group is that they are moving out of the age range of the paediatric department and great care must be exercised to ensure proper follow-up at a time when they are at greatest risk. Poor compliance early in filling is an absolute indication for surgical intervention.

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The Density of Cholinergic and Alpha and Beta Adrenergic Receptors in the Normal and Hyper-reflexic Human Detrusor

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Summary—The density of cholinergic and of alpha and beta adrenergic receptors was measured in samples of normal and hyper-reflexic human detrusor muscle. There was a significant reduction in the density of cholinergic receptors and a significant increase in the density of alpha adrenergic receptors in the hyper-reflexic samples as compared with normal. There was no difference between the two groups in the density of beta adrenergic receptors.

The physiological changes which occur in the hyper-reflexic bladder have not yet been fully elucidated. Differences between the normal and hyper-reflexic detrusor have been observed *in vitro* in a muscle strip experimental model (Kinder and Mundy, 1987) and *in vivo* using urodynamic assessment. The hyper-reflexic bladder has been shown to be more active than normal and is more likely, *in vitro*, to show spontaneous activity. One possible explanation for this hyperactivity is an abnormal density of autonomic receptors in the detrusor and the purpose of this study was to see whether such an abnormality exists.

Materials and Methods

Hyper-reflexia is here taken to mean the occurrence of urodynamically proven involuntary detrusor contractions in patients with no overt neurological disease. Biopsies of hyper-reflexic bladders were taken at the time of augmentation cystoplasty.

Normal bladder tissue was obtained at open operation from urodynamically normal young adults undergoing surgery for various unrelated urinary tract disorders.

The sex distribution was the same in both groups and the age range was similar. Bladder samples were always taken from the same site of the dome of the bladder and dissected free of serosa and mucosa, snap frozen in liquid nitrogen and stored at −70°C until the assay was carried out.

Each receptor assay was performed on 10 normal and 10 hyper-reflexic detrusor samples.

Cholinergic receptor assay (Levin *et al.*, 1984)

Each sample was rapidly weighed and homogenised in ice-cold 50 mM phosphate buffer, pH 7.4. The homogenate was passed through a double layer of gauze and protein content was assessed using a modified Lowry technique (Peterson, 1977) and used immediately for the receptor-binding assay.

The protein concentration of the homogenate to be used in the assay was adjusted to 1.0 to 1.2 mg/cm^3; 100 μl were incubated in the presence and absence of 10 μM atropine (the non-radioactive competitor) and varying concentrations of [^{3}H] QNB (quinuclidinyl benzilate, the specific radioligand), ranging from 0.05 to 40 nM (in a total volume of 300 μl). The specific activity of QNB used in this assay was 30 Ci/mmol. The mixture was incubated for 1 h at 25°C. The reaction was stopped by the addition of 4 cm^3 ice-cold buffer and the mixture was rapidly passed through a Whatman GFC glass fibre filter. The filter was washed with three 4-cm^3 aliquots of ice-cold buffer and placed in scintillation vials with 4 cm^3 scintillation fluid, triton-toluene

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scintillant, and the radioactivity was determined by scintillation spectrometry on an LKB-Wallac 81000 scintillation counter.

Alpha adrenergic receptor assay

The alpha adrenergic receptor binding assay was performed in a similar way, except that the buffer used throughout the assay was 50 mM Tris, pH 7.5, containing 10 mM Mg^{++}. The radioligand used was $[^3H]$ DHE (dihydroergocryptine) and the non-radioactive competitor was 10 μM phentolamine. Incubation was for 15 min at 30°C. The specific activity of the DHE used in this assay was 16.2 Ci/mmol.

Beta adrenergic receptor assay

The beta adrenergic receptor assay was performed as for the alpha adrenergic receptor assay, substituting $[^3H]$ DHA (dihydroalprenolol) as the radioligand and 10 μM propanolol as the non-radioactive competitor. The specific activity of the DHA used in this assay was 28 Ci/mmol.

The results of the scintillation counting were obtained as counts/min (CPM). These were converted to disintegrations/min (DPM) from a knowledge of the percentage counting efficiency and using a binding kinetics computer program. Using the protein concentrations determined by the modified Lowry technique, specific binding for the sample was calculated. The specific binding of the radioligand was determined by subtracting the amount of radioactivity bound in the presence of the non-radioactive competitor (non-specific binding) from the total binding in the absence of the non-radioactive competitor. The dissociation constant (Kd) and the maximum receptor density (Bmax) was calculated by Scatchard analysis (Scatchard, 1949) and by constructing Hofstee plots.

Results

There was a significant decrease ($P < 0.001$) in the density of muscarinic receptors in the hyper-reflexic group (23.10 fmol/mg protein) compared with normal controls (41.96 fmol/mg protein) (Fig. 1). There was a significant increase in the density of alpha adrenergic receptors in the hyper-reflexic group (38.22 fmol/mg protein) compared with the normal control samples (10.81 fmol/mg protein) (Fig. 2). There was no significant difference in the density of beta adrenergic receptors between the two groups (controls 7.49 fmol/mg protein, hyper-reflexic 4.57 fmol/mg protein) (Fig. 3).

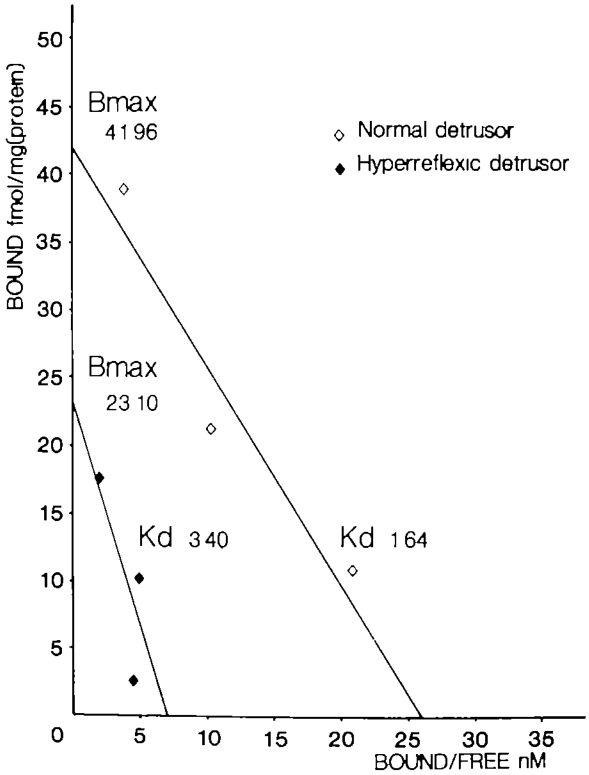

Fig. 1 Hofstee plot to show QNB binding in the normal and hyper-reflexic detrusor

Analysis of the specific binding at 0.5, 2 and 10 nM concentrations of QNB, DHE and DHA using the Mann-Whitney U rank sum test also showed there to be a significant difference in the density of muscarinic cholinergic receptors, and of alpha adrenergic receptors between normal and hyper-reflexic bladder muscle ($P < 0.001$). There was no significant difference in the density of beta adrenergic receptors in the normal and hyper-reflexic detrusor samples (Table).

Discussion

The human bladder was found to contain both cholinergic and adrenergic receptor sites.

The results show a significant decrease in the cholinergic receptor population and a significant increase in the number of alpha adrenergic receptors in the hyper-reflexic detrusor when compared with normal.

Care must always be taken with a study of this kind that conclusions are not drawn improperly. Although the density of receptors may be affected

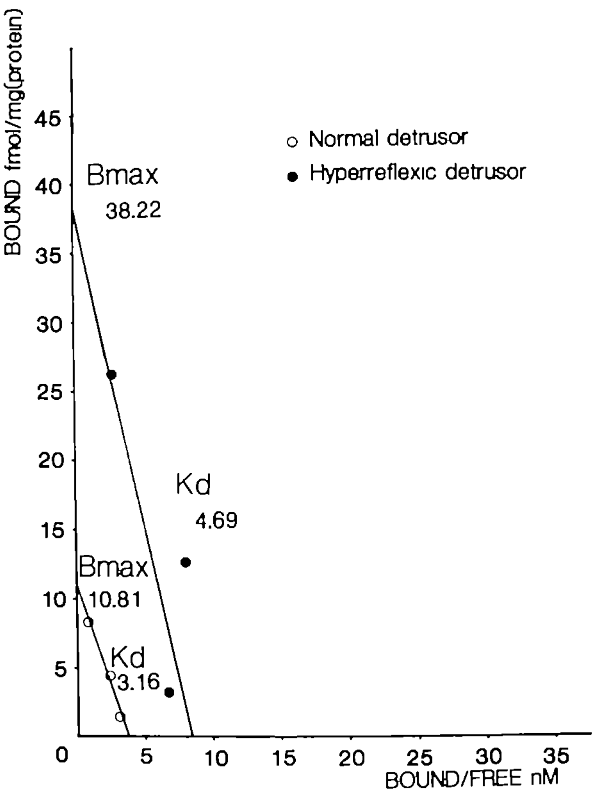

Fig. 2 Hofstee plot to show DHE binding in the normal and hyper-reflexic detrusor.

by changes in innervation, normal receptor density does not necessarily imply normal innervation or for that matter normal contractility in response to the binding of the relevant receptor agonist. However, the increase in alpha adrenergic receptors in the hyper-reflexic detrusor does correlate well with its behaviour *in vivo* and *in vitro*. *In vitro* muscle strips from hyper-reflexic bladders tend to be more active and are more likely to contract spontaneously than normal bladder strips (Kinder and Mundy, 1987). *In vivo*, the hyper-reflexic bladder is overtly overactive. With a greater number of alpha adrenergic receptors available for binding, this is what would be expected theoretically, although whether or not this is the explanation for the detrusor overactivity must remain open to question.

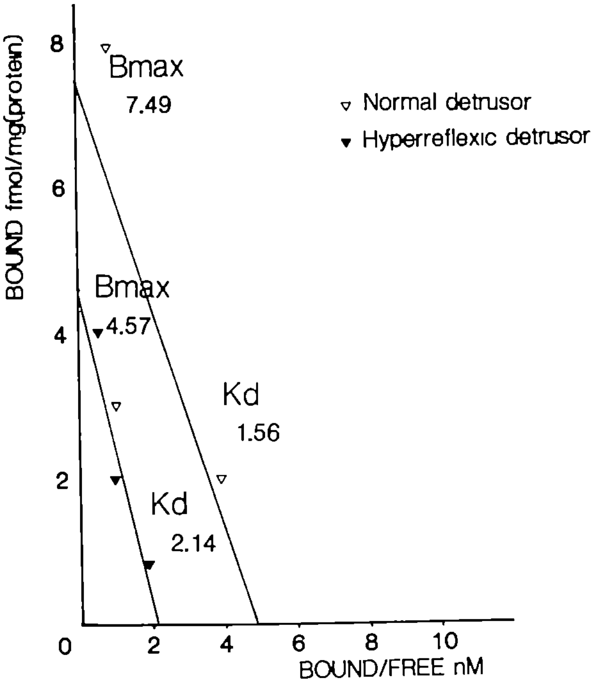

Fig. 3 Hofstee plot to show DNA binding in the normal and hyper-reflexic detrusor.

The decrease in the density of cholinergic receptors in hyper-reflexic detrusor samples is difficult to explain unless it is a direct result of the underlying disease. Otherwise it is tempting to suggest that it may be a form of regulatory mechanism to reduce overactivity in hyper-reflexia.

It appears that the density of beta adrenergic receptors is similar in both the normal and hyper-reflexic detrusor, which may indicate that they have little involvement in this disease.

Table Comparison of Specific Binding (fmol/mg protein) of QNB, DHE and DHA in the Normal and Hyper-reflexic Detrusor

Concentration of ligand (nM)	*QNB*		*DHE*		*DHA*	
	Normal	*HF*	*Normal*	*HF*	*Normal*	*HE*
10	38.13±3 62	17 60±2.20	8.08±1 46	26 15±4.92	7 85±2.82	4 01±0 52
2	20.82±1 74	10.12±0.76	4.40±0.94	12 96±1 60	3 04±0.46	1.97±0.19
0.5	10 17±0.86	2.36±0.69	1.43±0 44	3.17±0.43	1 94±0.41	0.91±0.16

HF—hyper-reflexic Mean±SEM

Thus hyper-reflexia is associated with a change in receptor density, at least part of which could be explained by a partial cholinergic denervation.

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Bladder Replacement by Ileocaeco-urethrostomy or Ileo-urethrostomy with a Reservoir after Cystoprostato-vesiculectomy for Bladder Cancer

A Functional Evaluation

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Summary—The purpose of this study was to evaluate the function of the intestinal segments used to replace the bladder after cystoprostato-vesiculectomy. The series included 30 patients, 10 of whom underwent clinical, radiological, urodynamic and electromanometric investigations. Seven patients had an ileocaeco-urethrostomy (ICUS) and 3 had an ileo-urethrostomy with a reservoir (IR).

The results were good in all patients and there was no sign of tumour recurrence. All were completely continent during the day but during the night only those who observed the 2-h intervals between voiding were continent. The radiological findings for 1 patient showed grade I asymptomatic vesicoureteric reflux. In all cases, periodic pressure waves were observed during electrocystomanometric tests at basal levels, with the IR patients showing waves higher in frequency and lower in amplitude. Prostigmin induced a significant variation in motor activity in IR patients only. The urodynamic tracings showed an almost physiological flow in both groups. Cystomanometry revealed good compliance in both types of new bladders. The height and width of contraction waves during filling was greater in ICUS than in IR patients. Good perineal sphincteric activity was demonstrated by electromyography. Low passive resistance was indicated by the urethral pressure profile.

Preliminary analysis of data indicated good functional micturition and renal function in both ICUS and IR patients. Slight differences were found between the two intestinal segments used for bladder replacement.

Bladder reconstruction was performed after cystoprostato-vesiculectomy (CVP) by ileocaeco-urethrostomy (ICUS) (Alcini *et al.*, 1985b) and by ileo-urethrostomy with a reservoir (IR). Slight modifications in the technique for the construction of the reservoir were the only differences from our previously reported surgical procedure (Alcini *et al.*, 1985a). The purpose of the study was to compare the motor and functional characteristics of the new bladders in ICUS and IR patients 2 years after surgery and to establish which procedure provided better functional micturition and renal preservation.

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Patients and Methods

Bladder reconstruction was performed on 30 male patients (age range 47–78 years) between 1980 and 1987; 26 underwent ICUS and 4 had IR. Both types of bladder were at first designed to contain about 150 ml of urine, since we noted a trend towards increasing the capacity up to 400 to 600 ml after 2 years.

A modification of our standard IR technique was used in order to reduce the risk of vesicoureteric reflux: an 8 to 10 cm afferent loop was dropped posteriorly to the reservoir (Fig. 1), creating an acute angle; as the new bladder refilled, the angle became more acute and thus acted as an antireflux device.

Electrocystomanometry (ECM)

Seven ICUS and 3 IR patients were evaluated by ECM 2 years after surgery. We used a catheter made up of 6 polyvinyl microcatheters (each with an external diameter of 1.2 mm and an internal diameter of 0.8 mm) with 1.0 mm^2 lateral holes, joined longitudinally (Fig. 2). The overall diameter of the catheter was 3.6 mm. Four recording points 5 cm apart were used: 2 inside the new bladder (1 as a back-up), 1 at the external sphincter and 1 in the urethra. The 4 channels were perfused with distilled water at a velocity of 1.0 ml/min using a low compliance system. The catheter was connected to a pressure transducer (Hewlett Packard 1280 Pressure Transducer) and to an 8-channel polygraph (Hewlett Packard 7758 D8 Channel Thermal Recording System) with a highly sensitive paper. Two additional channels with a valvular mechanism continually aspirated the fluids around the second recording channel in the new bladder, thus removing any perfused liquid and urine which accumulated during the examination. This maintained a constant quantity of fluid in the new bladder: about 20 ml after 6 months and about 40 ml 2 years after surgery. Following a bladder washout to remove all intestinal mucus, all patients were studied as follows: basal state recording for 120 min; recording for 30 min after a standard meal of 400 Kcal; recording for 45 min after an intramuscular injection of Prostigmin 0.5 mg.

Urodynamics (UDM)

The same patients who were examined by ECM were also evaluated urodynamically 2 years after surgery. A Life Tech 1153 Urolab was used, which gives simultaneous recordings of both electromyographic and pressure data. The following tests were performed: flow (Life Tech 1851 Flow Module); post-voiding residual by catheterisation; CMG of the new bladder (Life Tech 1851 CMG Module); abdominal pressure recorded using a

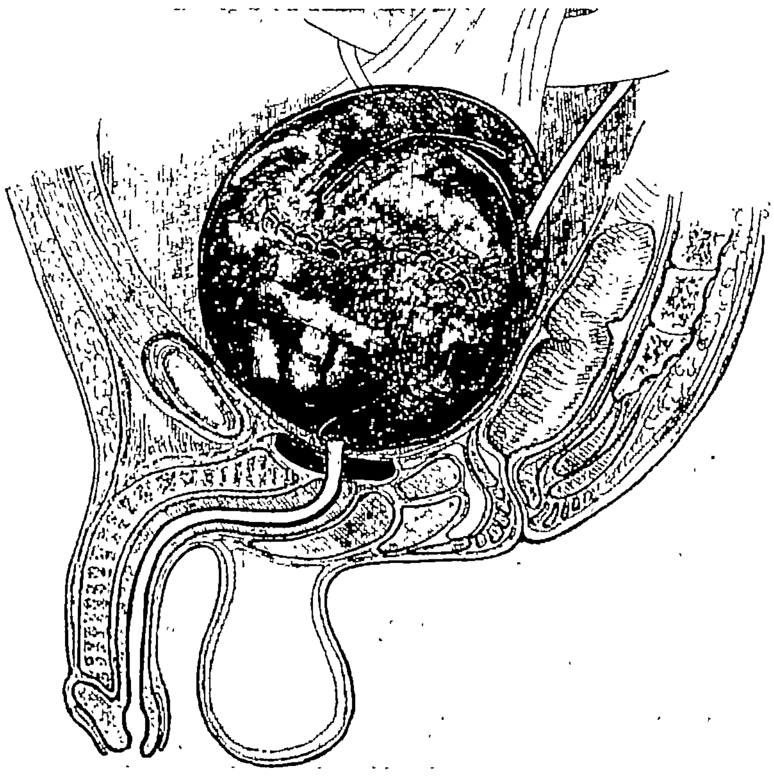

Fig. 1 Ileal reservoir. The long afferent ileal loop drops posteriorly to the reservoir, creating an acute angle which acts as an antireflux device.

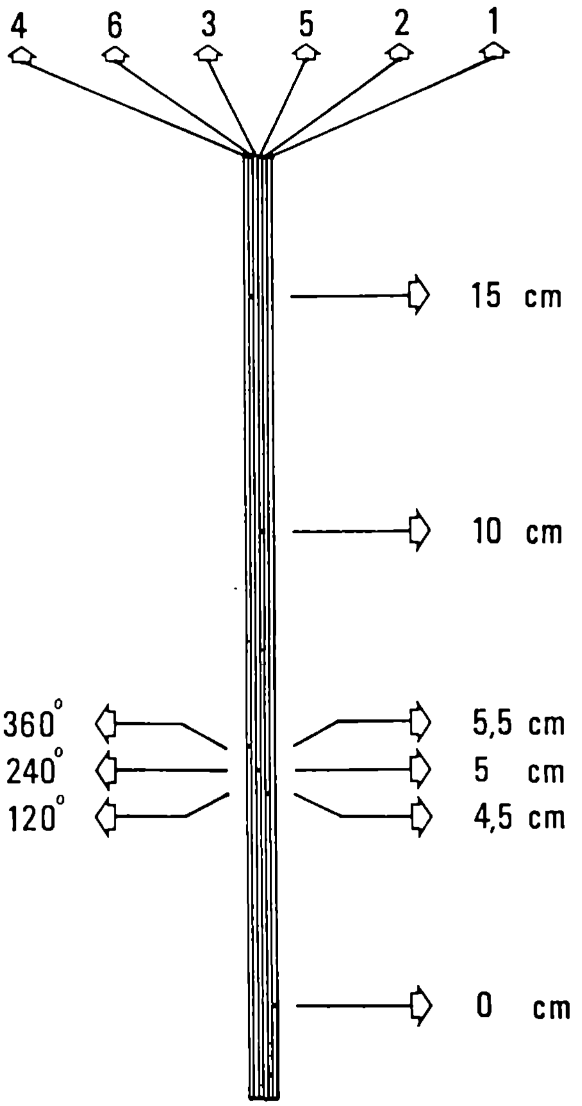

Fig. 2 The probe used for electrocystomanometric evaluation

rectal monitor; EMG of the perineal plane; ureteric pressure profile (UPP) (Life Tech 1852 Pressure Module). The refilling medium was physiological saline solution with a flow velocity of 60 ml/min for CMG and 40 ml/min for UPP. Abdominal pressure was measured using a rectal probe with an inflatable balloon inflated with 5 ml of water and positioned about 8 cm above the anal sphincter. The EMG was recorded using contact electrodes (Hewlett Packard) placed in the perineal region. At the time of the tests all patients had sterile urine. The tests were performed 2 h after waking, following a 12-h fast.

Results

Micturition and ureteric reflux characteristics ascertained by clinical and radiological investigation are shown in Table 1. Urodynamic results are given in Table 2 and Figures 3, 4 and 5. The ECM tracings for the ICUS patients 2 months postoperatively (Fig. 6) showed monophasic waves at rest with simultaneous relaxation of the external sphincter which caused small leaks of urine during the examination. This finding was no longer evident 2 years after surgery, probably due to the adaptation

Table 1 Urinary Function after 2 Years (10 patients)

	No. of patients									
	ICUS (7)							*IR (3)*		
Daytime voiding (7am–10pm)	4	4	5	4	6	4	5	5	4	4
Nocturia (10pm–7am)	4	4	5	3	0	5	4	4	5	3
Daytime incontinence	−	−	−	−	−	−	−	−	−	−
Enuresis (+, ±, −)	−	−	−	±	+	−	−	−	−	±
Urgency (+, −)	−	−	−	−	+	−	−	−	−	−
Urinary stream (+, ±, −)	+	+	+	±	+	+	+	+	±	±
Ureteric reflux (+, ±, −)	−	+	−	−	−	−	−	−	−	−
Renal function										
Improved										
Unchanged	U	U	U	U	I	U	U	U	U	U
Worsened										
Urinary tract dilatation	−	−	±	−	−	±	−	−	−	−
Reservoir dilatation trend	±	+	±	+	±	+	±	+	+	+
Residual urine > 30 cc	−	−	−	+	−	−	−	−	−	+

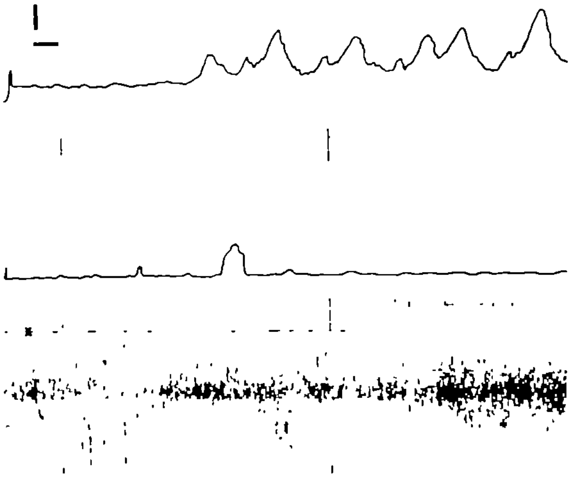

Fig. 3 Cystomanometry in ICUS patient. Horizontal bar = 0 5 mm/s Vertical bar = 1 cm = 20 cm H_2O × EMG = 1 cm = 10 mV.

Table 2 Urodynamic Testing

	ICUS							*IR*		
Flow										
Volume (ml)	280	180	320	350	200	190	210	300	340	250
Voiding time (s)	25	24	50	30	50	14	60	38	40	40
Peak flow (ml/s)	25	15	10	30	8	23	22	16	30	10
Residual urine (ml)	30	40	40	50	30	30	40	60	40	40
CMG										
Basal pressure (cm/H_2O)	10	12	8	8	10	12	12	8	6	8
First sensation (ml)	130	100	120	180	140	100	160	220	280	250
Leaks (Y/N)	N	N	N	N	N	N	N	N	N	N
Cough pressure (cm/H_2O)	16	12	8	8	30	8	12	40	14	20
Maximum capacity (ml)	340	300	360	400	360	400	470	460	650	600
UPP										
Peak pressure (cm/H_2O)	48	40	38	42	38	36	42	40	36	36
Occlusion pressure (cm/H_2O)	36	22	22	20	18	20	18	30	28	20
Functional length (mm)	18	18	18	16	16	18	16	18	20	18
Length continence area (mm)	8	6	6	4	4	6	8	6	6	5
EMG										
Increase in sphincter activity associated with uninhibited contractions	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y=yes. N=no

of the ileocaecal bladder to its new function as a urine reservoir and also to the improved competence of the external sphincter. Two years post-operatively the ECM tracings (Fig. 7) showed monophasic waves of clearly reduced amplitude compared with the tracings obtained 2 months after surgery. There were no statistically significant variations in the functional data recorded after a meal or after administration of Prostigmin when compared with basal data for the ICUS patients.

For the IR patients, the ECM tracings showed polyphasic waves (Fig. 8) having a higher frequency and a lower amplitude and width compared with the waves of the ICUS patients. After the administration of Prostigmin, IR patients had an increase in the total number of contractions, while the basal tone and wave amplitude did not show significant differences. Recordings taken after a meal revealed an increase in basal tone and a reduction in all other parameters: contractions/h; total duration of the contractions (expressed as a percentage of the time of observation); and amplitude of the contractions.

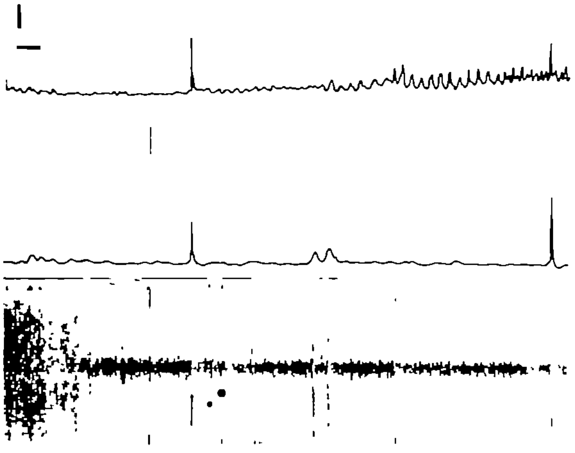

Fig. 4 Cystomanometry in IR patient. Horizontal bar= 0.5 mm/s Vertical bar=1 cm=20 cm H_2O ×EMG= 1 cm=10 mV.

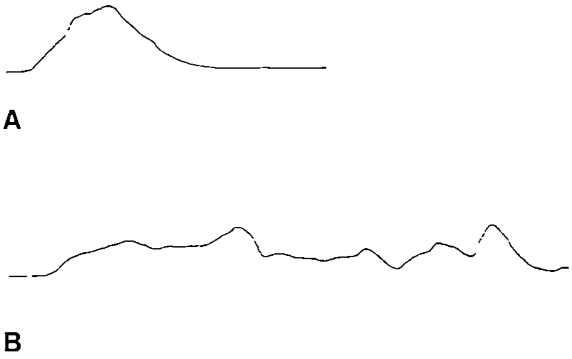

Fig. 5 Two flow recordings. Erect position, spontaneous micturition. (A) ICUS patient (erect position, spontaneous micturition volume 190 ml). (B) IR patient (Erect position, spontaneous micturition volume 300 ml). The flow is almost physiological in both cases

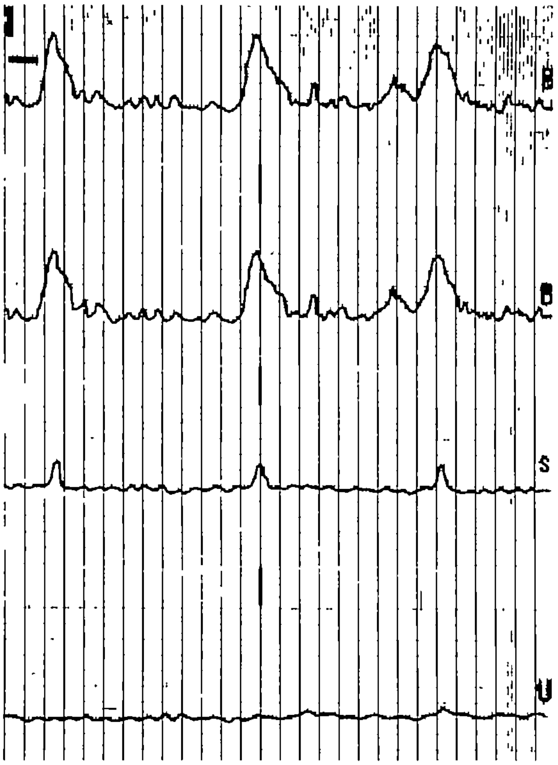

Fig. 6 ECM in ICUS patient 2 months after surgery Horizontal bar = 1 cm = 30 s Vertical bar = 1 cm = 20 cm H_2O B = bladder S = striated sphincter. U = urethra. The tracing shows the active contraction of the striated sphincter during the new bladder contraction waves.

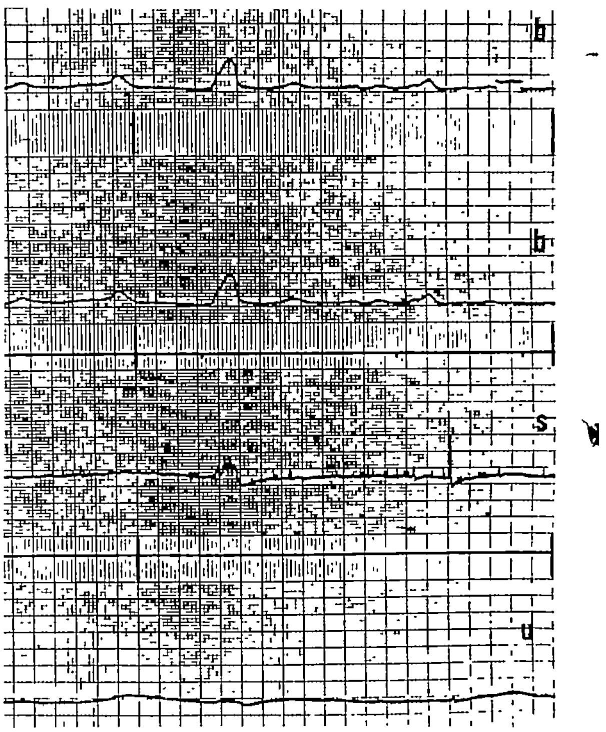

Fig. 7 ECM in ICUS patient 2 years after surgery. Horizontal bar = 1 cm = 30 s. Vertical bar = 1 cm = 20 cm H_2O. B = bladder S = striated sphincter. U = urethra. The tracing shows the clear decrease in the waves' frequency and pressure

Discussion

Interesting findings emerge from the quantitative and qualitative analysis of the data. In both types of new bladders, the urinary flow and emptying velocity were satisfactory. The UDM and ECM tracings seemed to demonstrate a greater force of contraction in the ICUS bladders and the incidence of enuresis was higher in these patients (Jakobsen *et al.*, 1987) than in the IR patients. Two years after surgery the ICUS bladders had a capacity of 400 to 500 ml and the IR bladders averaged between 500 and 600 ml. A longer latent period was found at the 2-year follow-up before the appearance of contraction waves.

Once initiated, the waves did not cause leakage of urine, as they had done at the 6-month follow-up. The absence of vesicoureteric reflux in 86% of the patients is indicative of the competence of the ileocaecal valve in ICUS patients (Kirby and Turner-Warwick, 1987) and of the efficacy of the acute angle between the new bladder and the

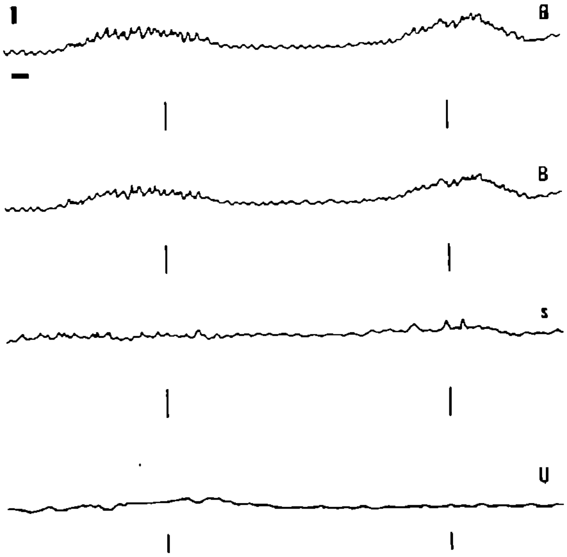

Fig. 8 ECM in IR patient 2 years after surgery. Horizontal bar = 1 cm = 30 s. Vertical bar = 1 cm = 20 cm H_2O. B = bladder. S = striated sphincter. U = urethra. The tracing shows polyphasic waves higher in frequency and lower in amplitude than in ICUS patients. No flow in the urethra.

afferent loop in IR patients. These antireflux mechanisms are adequate because of the satisfactory intervals between voiding and also because of the increased emptying facility allowed by the reduced passive urethral resistance.

The intervals between voiding, and voiding itself, were about the same for both ICUS and IR patients. We advise our patients to observe an interval of 3 to 4 h during the day and 2 h at night; if this advice is followed the patient will be completely continent. In fact, about 2 years postoperatively, the adaptation of the striated sphincter to its new function, the increased capacity and the decrease in motility of the new bladder allowed the patient to be continent for at least 2 h at night. Unfortunately, some patients preferred to be enuretic rather than interrupt their sleep. We feel that the achievement of satisfactory voiding, the preservation of renal function, the absence (or small volume) of residual urine and the absence of vesicoureteric reflux (Figs 9, 10, 11 and 12) are due to the radical extent of the surgical procedures and to good urethro-intestinal anastomosis. The execution of a CPV and the anastomosis between the intestine and the urethra reduce the passive urethral

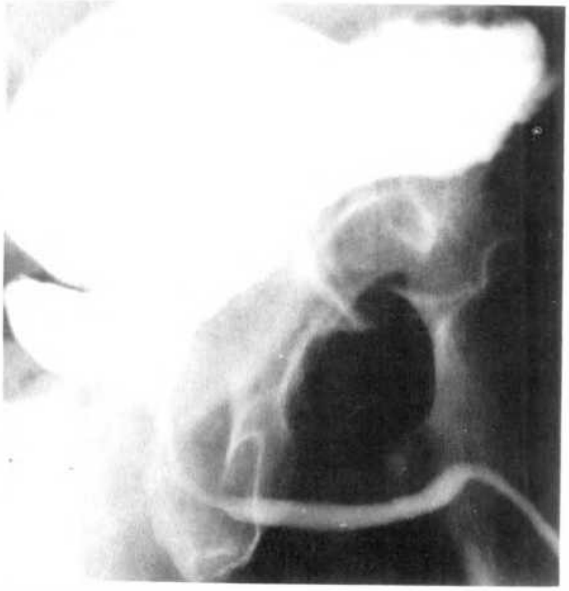

Fig. 10 Voiding cystography in IR patient 2 years after surgery does not show ureteric reflux.

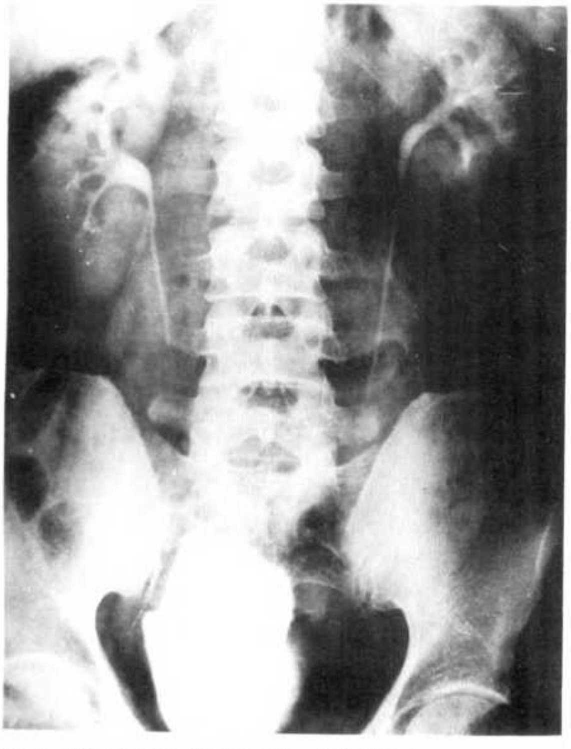

Fig. 9 IVU 2 years after surgery in IR patient.

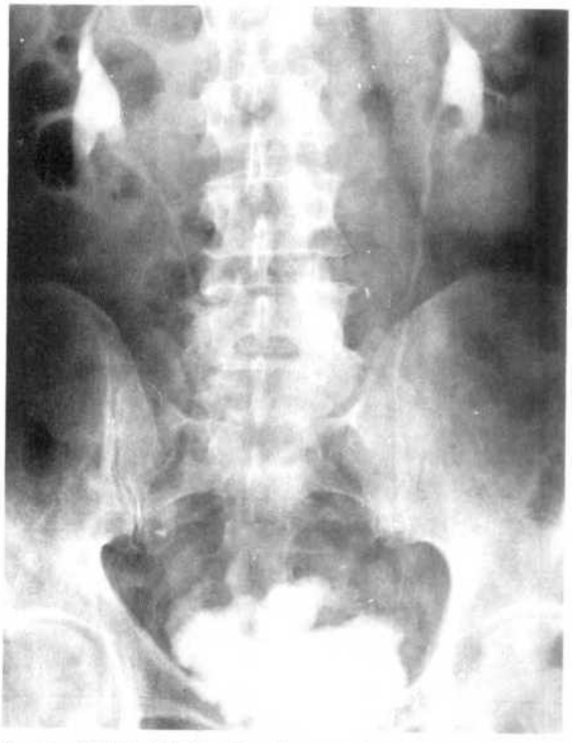

Fig. 11 IVU in ICUS patient 2 years after surgery.

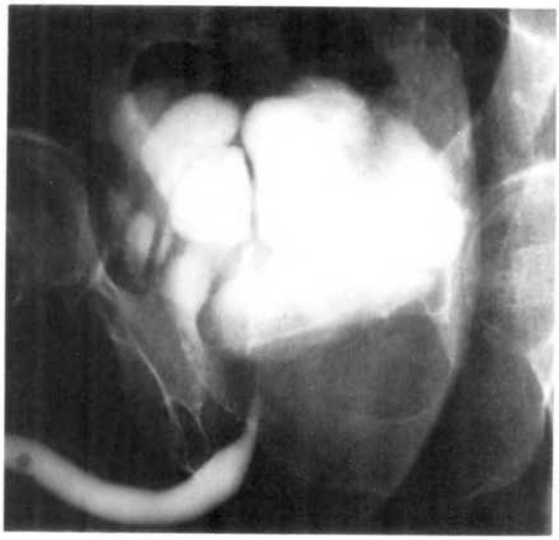

Fig. 12 Voiding cystography in ICUS patient 2 years after surgery. No ureteric reflux.

resistance in both ICUS and IR patients, as shown by the urodynamic investigations. We believe that ICUS and IR are valid therapeutic options for bladder replacement after cystectomy for cancer.

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Three Years' Experience with an Ileal Low Pressure Bladder Substitute

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Summary—At the beginning of this century it was realised that peristalsis would cause incontinence if bowel was used for augmentation or substitution of the bladder. Trans-section of the antimesenteric border and cross-folding of the intestinal segments (Goodwin's cup-patch technique) is an efficient means of solving this problem and has been successfully used in the Kock pouch.

We anastomosed the ileal low pressure reservoir to the membranous urethra in 22 male patients following radical cystoprostatectomy for bladder cancer. The mean observation time was 16 months (range 3–36). The capacity of the bladder substitute increased with time, the average being 450 ml after 6 months. In the first 4 patients with a short (2–5 cm) intestinal segment between the pouch and the urethra, micturition was prolonged, residual urine varied from 50 to 300 ml and bacteriuria was found. Occasional expulsions of several ml of urine were caused by peristalsis within this short tubular segment. In the following 18 patients, the low pressure reservoir was anastomosed directly to the membranous urethra. Micturition was good, with no notable residual urine, no bacteriuria and no paroxysmal urinary incontinence. However, a safety pad is used by half of the patients because once or twice a week, mainly at night, a few ml of urine may be lost. No significant changes in serum electrolytes, bicarbonate or creatinine were noted. With the three different antireflux techniques used, no obstructive or inflammatory changes in the upper urinary tracts were found, although no long-term antibiotic prophylaxis was given.

Interpositioning an ileal loop between the ureters and the stump of the membranous urethra after cystectomy was first used in animal experiments by Tizzoni and Foggi in 1888. Couvelaire (1950, 1951) published the first results with a U-shaped ileal urinary reservoir which communicated at its tip with the male urethra. Camey and Le Duc (1979) and Lilien and Camey (1984) used it for more than 25 years in male patients who underwent radical cystoprostatectomy.

When the tubular intestinal structure is left intact, an increase in volume results in pressure peaks caused by peristalsis (Mellinger and Suder, 1958). Thus incontinence is inevitable beyond a certain degree of filling. In part, this can be avoided by trans-section of the circular muscle fibres. In 1893, Rosenberg reported animal experiments in which he trans-sected the antimesenteric border of an ileal loop used for bladder augmentation. Rutkowski (1899) used this technique in a patient with bladder exstrophy.

The essential progress towards an intestinal low pressure reservoir, however, was the cup-patch technique described by Goodwin *et al.* (1959). They used it for bladder augmentation. Not only was the antimesenteric border of the bowel trans-sected but, by opposing the ileal segments in different directions, the reconstruction of a functionally tubular structure (although larger) by interconnecting the circular fibres could be avoided and a more spherical compartment was created.

The superiority of the cup-patch technique over a non-split ileal segment or a split but retubularised intestinal loop with regard to pressure peaks was

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confirmed by Ekman *et al.* (1964) and Kock (1969) and is used for the creation of the Kock pouch reservoir.

We tried to combine the advantages of the Kock pouch (low pressure reservoir) and the Couvelaire/ Camey procedure (use of the male patient's own sphincter system) while obviating their shortcomings (avoidance of the distal nipple and stoma which need to be catheterised repeatedly and which may cause problems requiring further surgery; avoidance of the nocturnal incontinence owing to high pressure waves in patients with an ileal loop anastomosed to the urethra).

Our preliminary animal experiments were performed in 1983 and 1984 (Studer *et al.*, 1985). Based on these results and this experience, the technique was slightly modified and applied in male patients who underwent radical cystoprostatectomy for bladder cancer.

Patients and Methods

Between 1985 and 1987, intestinal low pressure substitutes were performed in 22 male patients with bladder cancer who required radical cystectomy. Their mean age was 66 years (range 56–80). In all cases the pre-operative biopsy from the prostatic urethra was negative for cancer and no distant metastases were detected. One patient had had 65 Gy of photon radiotherapy for prostatic cancer 3 years earlier. Their serum creatinine was between 80 and 130 µmol/l.

Surgical technique

Following regional lymph node dissection and provided that no lymph nodes with macroscopically evident metastatic involvement are found, cystoprostatectomy is performed in the usual way: following ligature and trans-section of the superior vesical arteries, the dorsal and dorsolateral vesical pedicles are progressively severed: in the deep presacral area on the side of the bladder cancer, along the pre- and para-rectal areas (leaving the pelvic plexus untouched) on the contralateral side. After incising the pelvic fascia in the lateral paraprostatic areas and cutting the pubo-prostatic ligaments, the superficial and deep veins of Santorini's plexus are ligated and divided according to the technique of Walsh (1986). The membranous urethra is trans-sected as close as possible to the apex of the prostate, usually across the colliculus seminalis. The prostatic pedicles are progressively cut close to the prostate capsule, in order to preserve the para-prostatic neurovascular bundles.

Approximately 25 cm from the ileocaecal valve an ileal segment 50 to 65 cm in length (depending on the anti-reflux technique used, see below) is isolated and the bowel continuity is restored with a 4/0 single layer suture (polyglycolic acid). For construction of the pouch, the distal 40 cm of the isolated ileal segment are opened with scissors along the antimesenteric border. Both ends are closed by a running suture (Fig. 1A). If the intussuscepted ileal nipple is used as an antireflux valve, it is performed as described by Kock *et al.* (1982) and Skinner *et al.* (1984), with a few modifications: the nipple is outside the pouch in the proximal afferent ileal limb ("triple nipple"). The mesentery of the intussuscepted part is freed of fatty tissue but the vessels are not severed (Fig. 1B). No staples are used, but non-absorbable polypropylene sutures 2/0 between the seromuscular layers of the inner and medial part are inserted. For the construction of the triple nipple approximately 15 cm are needed and for implantation of the ureters into the most proximal end, another 3 to 4 cm of tubular ileum are needed. The ureters are stented and 4/0 polyglycolic acid sutures are used for the ureteric anastomosis.

For construction of the pouch, the two medial borders of the U-shaped ileal segment are oversewn by a single layer seromuscular continuous suture (2/0 polyglycolic acid) (Fig. 2A). Thereafter, the bottom of the U is placed between the two ends of the U on the patient's right side (Fig. 2B) and the lower half of the pouch is closed again with a single layer continuous suture. A hole with a diameter of 5 to 6 mm is cut into the lowest part of the pouch wall and anastomosed with 6 polyglycolic acid 2/0 sutures to the membranous urethra over an indwelling 18F silicon catheter (Fig. 3A). Before closure of the cranial part of the pouch, the ureteric stents are passed through its wall and a "cystostomy tube" (22F silicon catheter) is inserted, serving as a safety outlet in case the urethral catheter is obstructed by mucus clots (Fig. 3B).

Two other forms of anti-reflux mechanisms were used on a random basis (Fig. 4):

The split-cuff technique as described by Griffith and Turner-Warwick: the distal ureters are split and everted (Turner-Warwick and Ashken, 1967). Provided the ureters are sufficiently long, this technique makes it possible to use a short proximal ileal limb of 4 to 6 cm only (Fig. 4B). In these patients the total length of the resected ileum is approximately 50 cm.

A proximal tubular isoperistaltic ileal limb 18 to

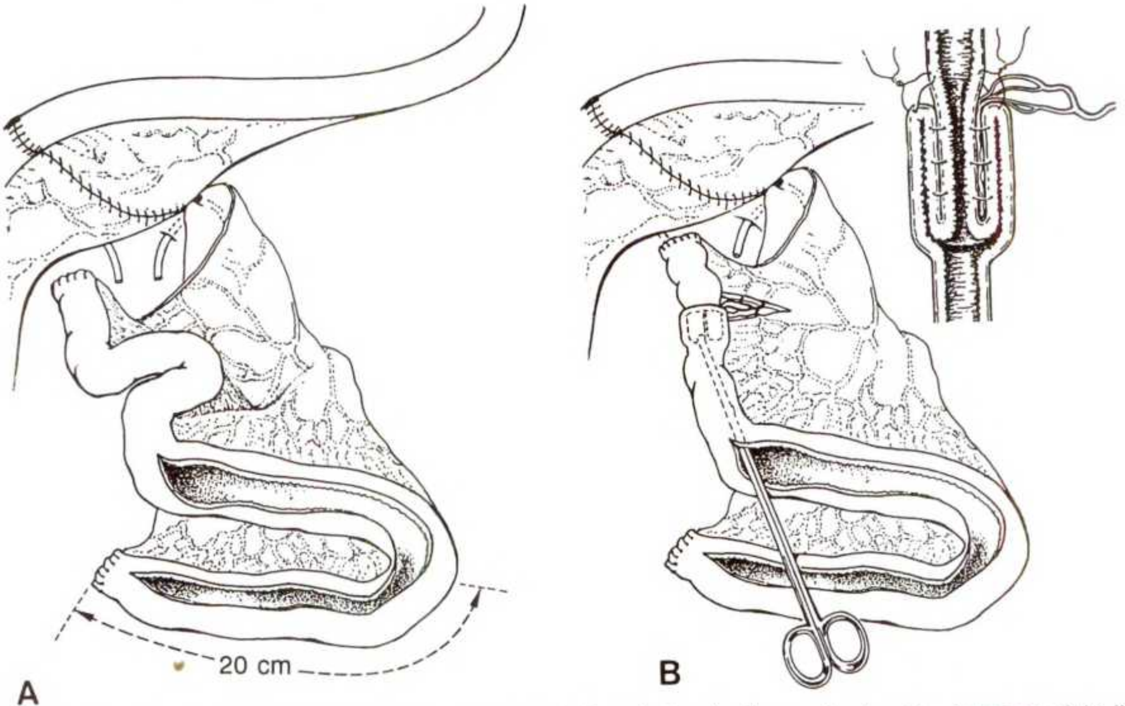

Fig. 1 (A) Excision of a 50–65 cm ileal segment approximately 25 cm before the ileocaecal valve. The distal part of the ileal segment is opened along the antimesenteric border, thus creating the U-shaped segment measuring 2 × 20 cm. Both ends are closed. (B) The mesentery of the intussuscepted part is freed of fatty tissue before creation of the antireflux nipple.

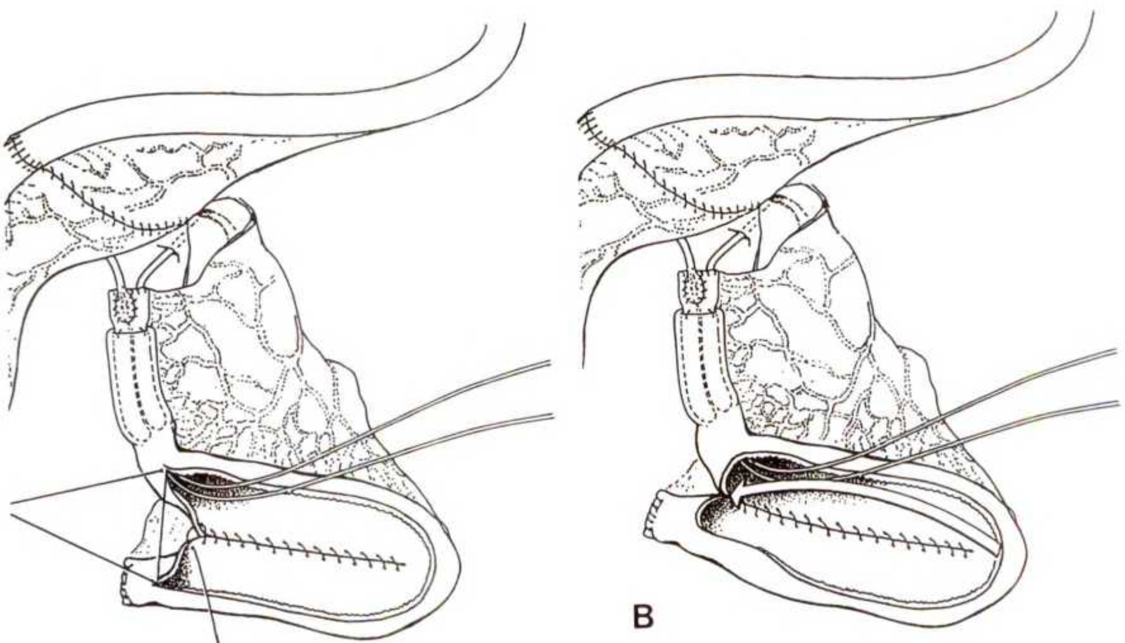

Fig. 2 (A) The ureters are anastomosed and stented. Closure of the posterior wall of the pouch by oversewing (single layer, seromuscular continuous suture) the two medial borders. (B) The bottom of the U is flipped over between the two ends of the U.

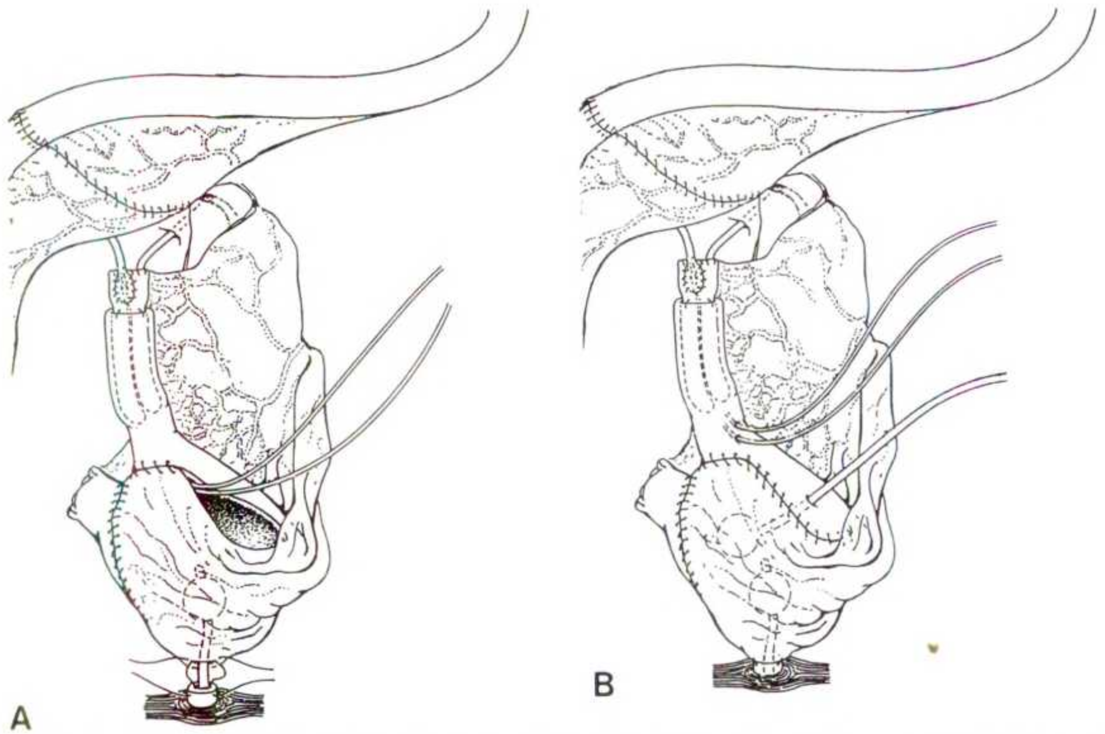

Fig. 3 (A) After closing the lower half and part of the upper half of the anterior wall by continuous suture, anastomosis of the lowest part of pouch to the membranous urethra is performed. (B) The ureteric stents are passed through the pouch wall and a "cystostomy" is placed in it. Closure of the cranial part of the pouch.

20 cm in length between the ureters and the pouch (similar to an ileal conduit) (Mann and Bollman, 1931) (Fig. 4C).

Post-operatively, the pouch is rinsed every 6 h with saline through the "cystostomy" and the urethral catheter; mucus clots must be aspirated. Between the tenth and twelfth post-operative days the ureteric stents are removed. After exclusion of a fistula by a "cystogram" on the fourteenth day, the "cystostomy" is removed and 3 days later the urethral catheter. Patients are instructed to void in the sitting position, relax the pelvic floor and expel urine by abdominal straining. They are followed up every 3 months. Creatinine, sodium, potassium, chloride, and bicarbonate are determined in the serum. Residual urine or dilatation of the upper urinary tracts are checked by ultrasound or IVU and a urinary culture is done.

Results

The average operating time to create a low pressure reservoir with anastomosis to the urethra is 30 to 40 min longer than for a standard ileal conduit. If the antireflux triple nipple is used, an additional 15 min are needed.

A major complication with the pouch occurred in 1 patient. Because of partial necrosis, the pouch was replaced by an ileal conduit 3 months post-operatively.

All patients were able to void, first in a sitting, later in an upright position. However, the first 4 patients with a short tubular intestinal segment between the pouch and the urethra (Fig. 5A) had prolonged micturition and chronically infected residual urine, varying between 50 and 300 ml. Moreover, these longer periods (varying between 2 and 24 h) of absolute continence were followed by a sudden expulsion of 2 to 10 ml of urine into the urethra, day or night. Urodynamic studies ruled out stress incontinence, but within the short tubular intestinal segment between pouch and urethra, pressure peaks with values up to 80 cm H_2O were noted, although the pressure values within the pouch varied between 5 and 35 cm H_2O only at these times and when filled to capacity (Fig. 5D). Fluoroscopy showed peristalsis in the distal limb

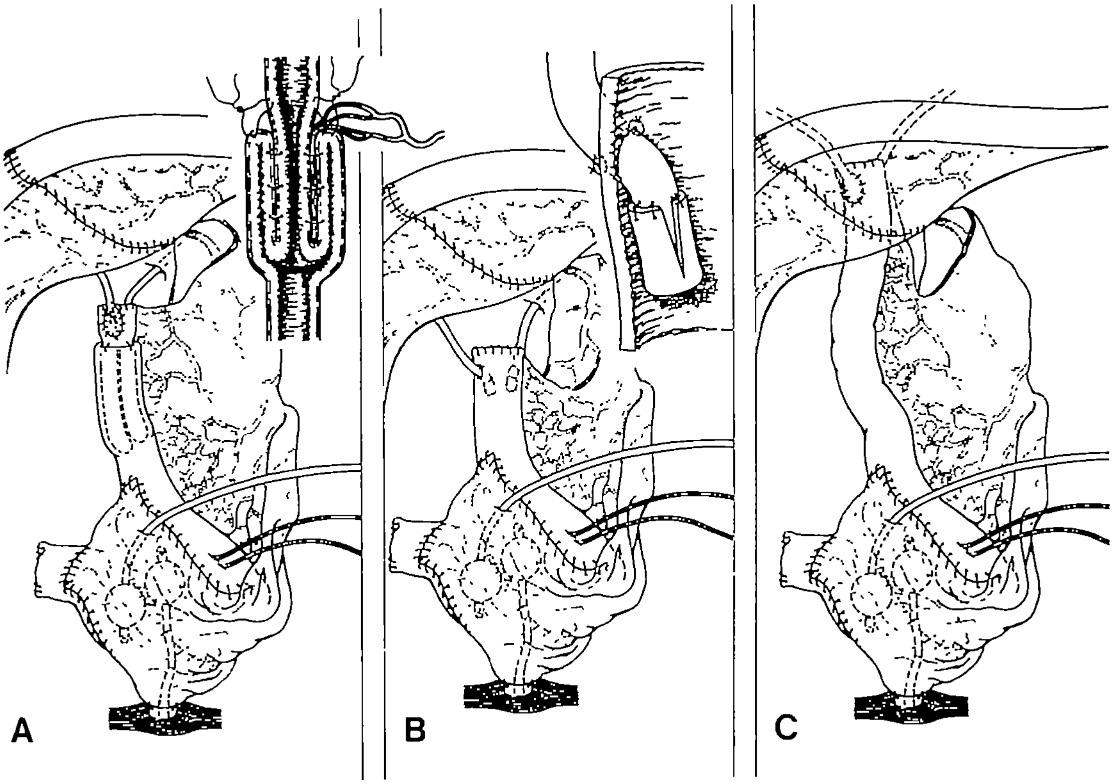

Fig. 4 In addition to the triple nipple (A), two other antireflux mechanisms were randomly used. the split cuff technique of the ureters (B) or a tubular, isoperistaltic proximal limb of 20 cm (C). With the split cuff technique, the minimal length of the afferent ileal limb is 4 to 6 cm, thus the total length of excluded ileum is only about 50 cm.

when the pressure peaks appeared and the contrast medium which it contained was expelled into the urethra. Because of the paroxysmal incontinence and the voiding difficulties, the distal tubular limb between pouch and urethra was resected in 2 of these 4 patients after 18 and 30 months and the pouch was anastomosed directly to the urethra. Thereafter, micturition was good without residual urine in both patients. Attacks of sudden incontinence were no longer observed.

In the 18 patients without a short tubular intestinal segment between the pouch and the membranous urethra (Fig. 5C), voiding was good with flow peaks of up to 30 ml/s. No residual urine exceeding 20 ml was observed and the urine was sterile in 10/12 patients examined repeatedly for more than 6 months. In 17 of these 18 patients, diurnal and later nocturnal continence improved within the first post-operative months and paralleled the increase in the pouch's capacity: during the day, continence was good after 3 to 6 months and 8/12 patients wore no safety pad after that time. During the night, however, this continues to be worn by some patients, because 5 to 10 ml of urine may be lost between 1 and 12 times per month. When sleeping deeply, the patients do not always wake up when the reservoir is full, but only when some urine passes into the urethra. The 5 patients with preserved potency recovered faster. One patient has stress incontinence grade I which is gradually improving; he suffers from peripheral neuropathy. None of our patients uses an incontinence device or an anticholinergic drug for suppressing the peristaltic activity of the bladder substitute.

After 6 months, the mean micturition volume was 450 ml, diurnal frequency was 4 to 7 times and nocturia 1 to 3 times; when filled to capacity, pressure within the pouch varied between 20 and 35 cm H_2O, caused by asynchronous wall contractions. Without long-term antibiotic prophylaxis, no patient had clinical signs of pyelonephritis or ureteric obstruction, regardless of the various forms of antireflux procedures used (Fig. 6A). Regardless of the antireflux mechanism used, cystography

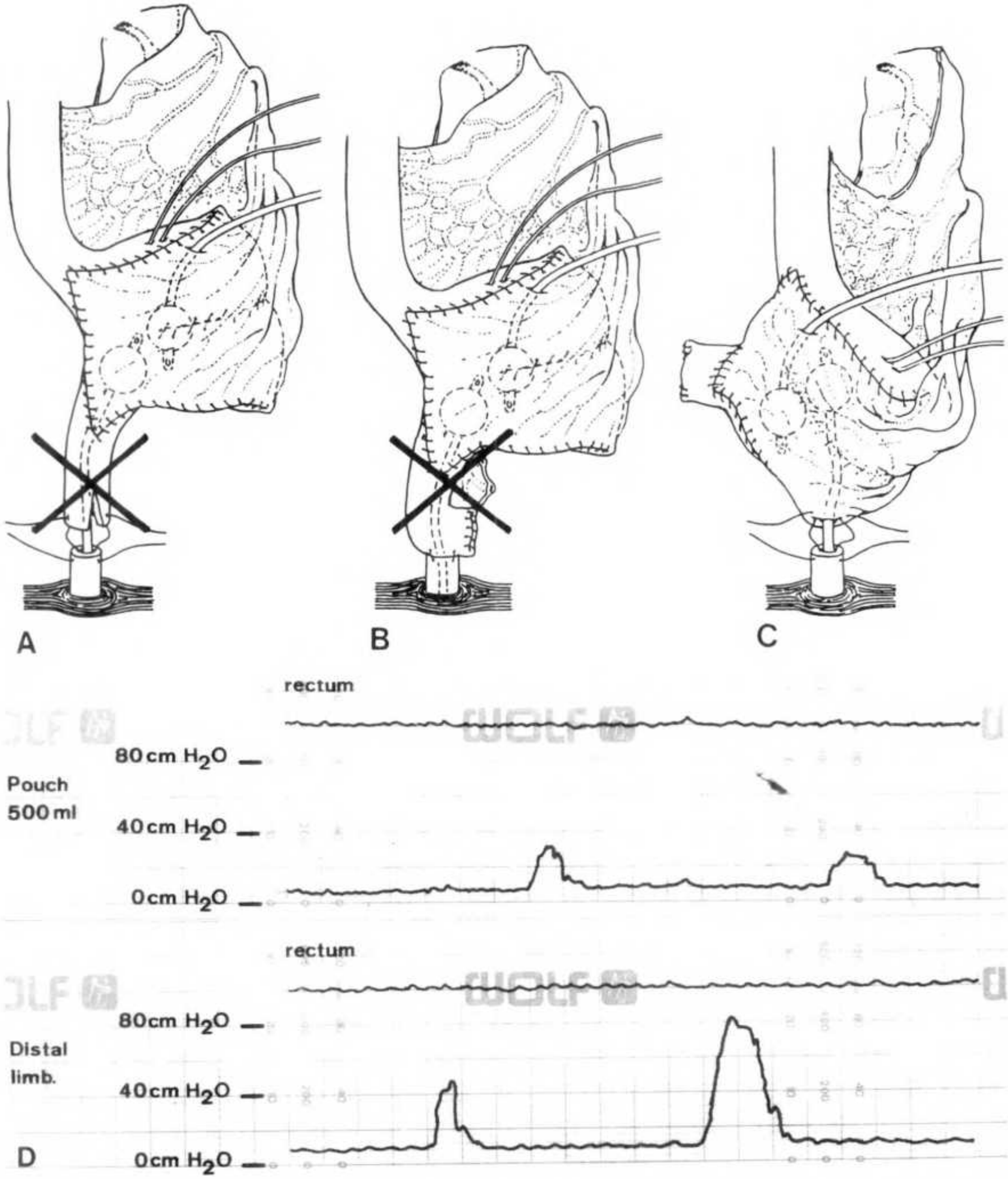

Fig. 5 It is essential to anastomose the lowest part of the low pressure pouch directly to the membranous urethra (C). The technique shown in (A) and (B) with a short tubular segment between the pouch and membranous urethra is not recommended. Peristalsis within this distal tubular segment results in intermittent incontinence due to pressure peaks of 80 cm H_2O, although the pressure within the pouch remains below 40 cm (D).

showed reflux into the proximal ileal limb of the pouch but never up to the kidneys (Fig. 6B).

During follow-up there was no significant change in serum creatinine, electrolytes or bicarbonate and no substitution was needed; 18/22 patients noticed an increased fluid intake of 1.8 to 2.7 l/24 h. After 24 to 30 months, this gradually decreased to preoperative levels and was paralleled by diminished mucus production in the bladder substitute.

All patients pursue their previous activities without restrictions, except for 2 who died from progressive disease and 4 others suffering from metastases. So far, no recurrence has been found in the urethra.

Discussion

During the last 100 years, many forms of bladder augmentation plasty and substitution have been described. Reports of satisfactory long-term results have been less frequent and so we deferred the presentation of our technique until some patients had been followed up for at least 3 years. Moreover, although we started the animal experiments with the combination of the Kock and Camey procedures (Camey and Le Duc, 1979; Kock *et al.*, 1982) before they became widely known (Lilien and Camey, 1984; Skinner *et al.*, 1984), our experience with 22 patients is limited: we deliberately avoided performing the operation in too many patients within a short period of time in case there were significant complications. Indeed, after observing the first 4 patients for 1 year, we had to modify the technique by omission of the distal limb (Fig. 5). Although our main goal was to create a low-pressure reservoir based on Goodwin's cup patch technique in order to prevent high pressure peaks, we learned that even a small tubular segment 2 to 5 cm in length between the pouch and membranous urethra could cause intermittent peristaltic waves with urinary incontinence.

To achieve continence, the pressure within the

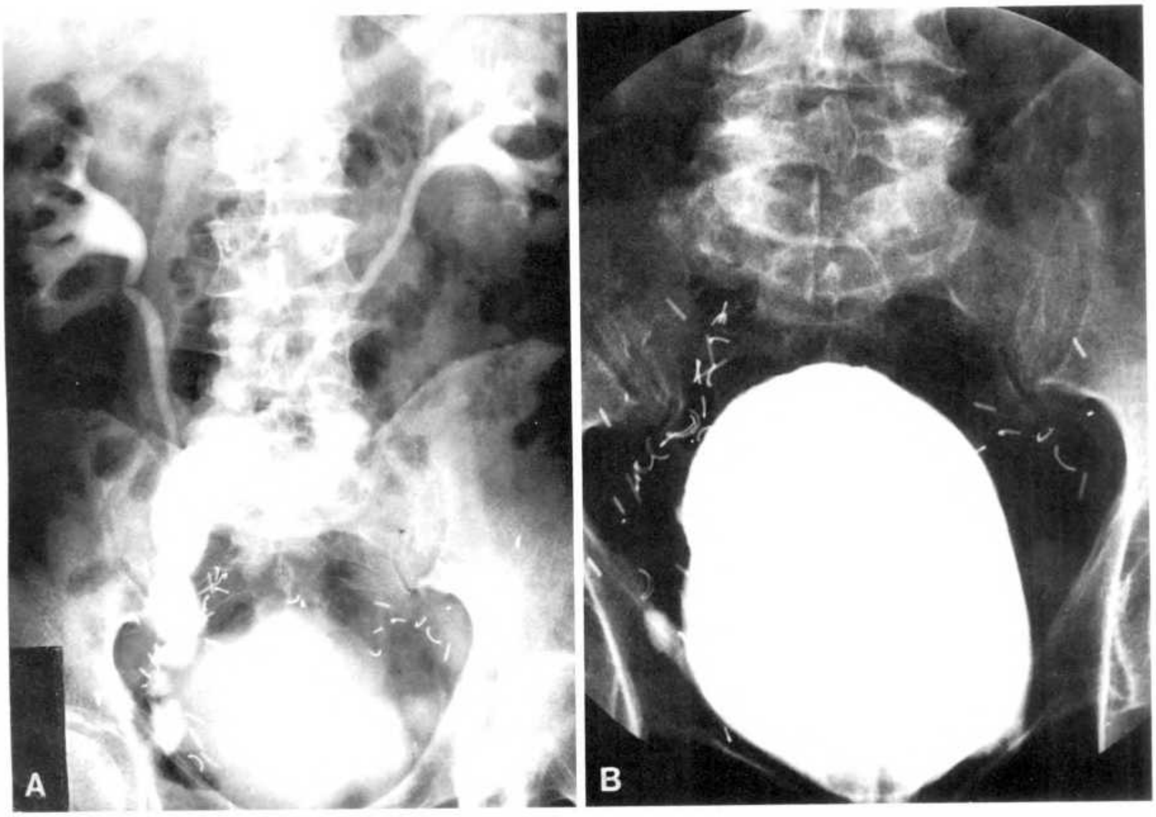

Fig. 6 (A) IVU of a patient with an ileal bladder substitute and no antireflux mechanism other than a 20-cm isoperistaltic ileal segment (schema Fig. 4C). Note the irregular shape of the proximal tubular limb due to peristalsis, whereas the wall of the bladder substitute is regular. (B) Cystogram of the same patient. Reflux is seen only into the most distal part of the proximal tubular ileal limb when filled to capacity, not reaching the ureteric anastomosis.

urinary reservoir must stay permanently below the resting tonus of the urethra, *i.e.* below 40 cm H_2O. This is the case for all forms of intestinal bladder substitute, as long as they are empty, and applies also to the tubular ileal loop. However, the pressure characteristics when the bladder substitutes are filled to capacity are decisive for continence, namely whether pressure peaks (induced by distension of the intestinal wall) which exceed the sphincteric pressure occur because of peristalsis. They can exceed 100 cm H_2O in an ileal loop and this must result in incontinence (Mellinger and Suder, 1958; Ekman *et al.*, 1964; Camey and Le Duc, 1979). The frequency of incontinence could be reduced to a certain extent by using longer loops, but this could not prevent high pressure peristalsis when they are filled to capacity. In our patients, the pressure waves did not exceed 35 cm H_2O when filled to capacity (Fig. 5D) 6 months after surgery, which is consistent with Norlén and Berglund's findings in the Kock pouch (Norlén and Trasti, 1978; Berglund *et al.*, 1984). It is not only important to trans-sect the circular muscle fibres (split ileum also retains its motor activity (Rosenberg, 1893)) but to have 4 intestinal segments per cross section (Goodwin's cup-patch technique (Goodwin *et al.*, 1959)). Because of Laplace's law (tension of the wall = pressure × radius) the intraluminal pressure is significantly lower than that found in a tubular ileal segment with identical tension in its wall (Fig. 7); also, peristalsis of one of the intestinal wall segments results in a markedly lower pressure increase and Laplace's law explains why improvement in continence during the first post-operative months depends on the increasing pouch volume (decrease of intraluminal pressure). Finally, transformation of a tubular structure into a spherical one results in higher volume, although the surface remains the same (Fig. 7).

Despite the construction of a low pressure bladder substitute, stress incontinence may occur. No reconstructed bladder neck, such as after a radical prostatectomy, can compensate partially for incompetence of the external sphincter. Therefore, when dissecting the apex of the prostate, the maximum possible length of the functional membranous urethra should be preserved. Nevertheless, no prostatic tissue is left which could cause mechanical outlet obstruction, infected residual urine or urinary retention. According to our experience, it is possible that preservation of the paraprostatic neurovascular bundles responsible for erection (Gosling, 1979; Walsh, 1986; Schlegel and Walsh, 1987) will improve continence. However, to avoid injury to the neurovascular bundle more cranially, resection has to be rather close to the seminal vesicles, and therefore to the bladder wall. Because this could compromise radical surgery, we avoided it in patients with T3b lesions, at least on the side of the tumour. Concern about compromising radical tumour surgery also made us reject a bladder substitute in female patients. In order to have satisfactory continence, the urethra and bladder neck (as well as the anterior vaginal wall) would have to be preserved. This would result in a bladder augmentation procedure and not in a bladder substitute.

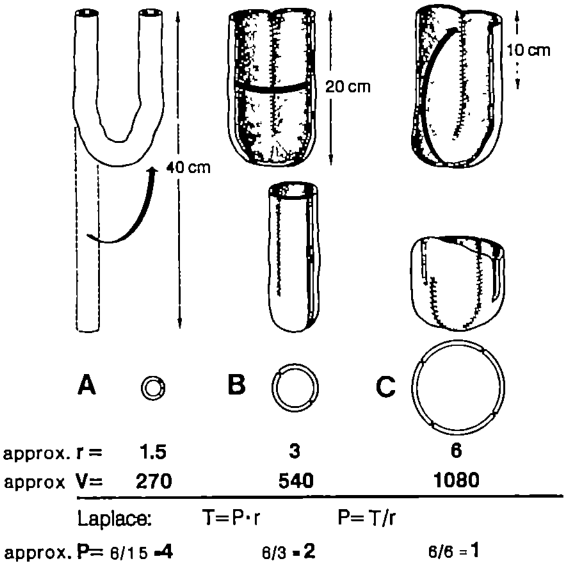

Fig. 7 (A) Theoretical aspects of various cylindrical reservoirs made from a 40-cm tubular (ileal) segment with a diameter of 3 cm (B) If the antimesenteric border is split and a tube (also larger) is recreated, the volume is doubled (C) If the intestinal segments are crossfolded according to Goodwin's cup-patch technique, the volume is 4-fold. Accordingly, the pressure decreases for equal tension of the wall (law of Laplace, see text). V = volume, T = tension, P = pressure, r = radius

Construction of an antireflux mechanism in patients with a (tubular) high pressure reservoir is essential. It is not known whether this is also needed in patients with bladder substitutes having pressures below 40 cm H_2O and being directly anastomosed to the urethra, thus acting as a safety valve with the external membranous sphincter. None of the 8 patients with neither an intestinal nipple nor split-cuff ureters, but with an 18 to 20 cm isoperistaltic intestinal segment between the ureters and the pouch (Fig. 4), had a history or radiographic signs of pyelonephritis. A tubular isoperistaltic bowel segment is supposed to have a certain antireflux effect as well, at least under slow (physiological) filling conditions of the pouch and in a low pressure system. This is suggested by our urodynamic and fluoroscopic findings. Indeed, in 1931 Mann and Bollmann found that an ileal segment 15 to 20 cm in length could prevent the passage of fluid in the antiperistaltic direction. For urinary diversions, their technique had first been used by Gilchrist *et al.* (1950). However, because their pouch was a high pressure system, the antiperistaltic ileal segment could exert only limited antireflux properties. More experience with this technique is needed before a definitive answer can be given.

The absence of urinary obstruction in 7 patients with a "triple nipple" (Fig. 4A) seems to indicate that the intraluminal pressure within it is not too high. When compared with Kock's intussuscepted nipple with 2 layers, the advantage is its location outside the pouch and thus prevention of protrusion towards the outlet of the bladder substitute (resulting in urinary retention). In addition, the non-reabsorbable material (seromuscular sutures between the inner and middle intestinal wall) maintains the nipple in its position, without being in contact with urine. The formation of stones or chronic infections can thus be avoided. Although Skinner *et al.* (1987) had excellent medium-term results after stripping off the mesentery from the intussuscepted part, we hoped to prevent atrophy due to chronic ischaemia (resulting in incompetence of the nipple) by preserving the major vascular branches. Nevertheless, it remains to be seen whether this and the triple nipple technique, which we used also for the outlet valve of the Kock pouch, will reduce the occurrence of secondary nipple incompetence.

The capacity of the reservoir increased within the first months to that of normal bladders, although only 35 to 40 cm of ileum were used. The relatively small surface of intestinal mucosa may be the reason for our having observed no impaired electrolyte balance or metabolic acidosis. Skinner *et al.* (1987) made the same observation in 250 patients with a Kock pouch made from a similar length of ileum. However, we do not recommend the ileal bladder substitute in patients with a serum creatinine >150 μmol/l. Jagenburg *et al.* (1978) noted a reabsorption of acids by an ileal reservoir and also found that iso-osmolality between urine and serum was established within 2 to 6 h. This is mainly achieved by a transmucosal shift of free water into the pouch. This explains why our patients felt thirstier after surgery and why they should be advised to drink 2 to 3 litres of water each day (Kerr *et al.*, 1959). The rapid shift of free water into the pouch is the reason why patients with an intestinal bladder substitute have to void 1 to 1.5 litres of urine per night, resulting in nocturia. Restriction of fluid intake in the evening would not alter this physiological phenomenon but would result in dehydration and hyperosmolality in the serum and must therefore be avoided. Construction of a larger pouch in order to increase its capacity and prevent nocturia would increase the storage time of urine and the intestinal surface. More urinary solutes and acids would be reabsorbed, resulting in an increased risk of metabolic disturbance (acidosis, hyperammonaemia) and renal failure.

When comparing our technique with those using the ileocaecal segment, the following advantages are found: by preserving the most distal part of the terminal ileum, the resorption of vitamin B_{12}, folic acid and biliary acids should be compromised less, and the ileocaecal valve is left intact. Moreover, a small bowel anastomosis is believed to have a lower risk of complications than an ileo-ascendostomy. In addition, omission of a large bowel segment could result in less secretion of mucus into the pouch. According to Berglund *et al.* (1984), caecal reservoirs also have lower distensibility and more motor activity.

After a maximum follow-up of 3 years, it was concluded that the results with our low pressure ileal bladder substitute are promising. The procedure is easy to perform and could form an alternative to cutaneous urinary diversion in selected male patients requiring radical cystoprostatectomy.

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The Mitrofanoff Principle for Continent Urinary Diversion

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Summary—A continent urinary diversion was formed for 16 patients using the Mitrofanoff principle for continence. As originally described, this system used the appendix tunnelled into the bladder to form a continent catheterisable vesicostomy. We have expanded the technique and have used all available narrow tubes as continent conduits (ureter 10 cases, appendix 5, Fallopian tube 1). The urine container was made of large and small intestine and bladder in several combinations. The system has been very satisfactory: 14 patients were continent and able to catheterise; 1 required a revision to achieve continence and 1 awaits revision; 3 patients required revision procedures for stricture.

For any reconstruction of the lower urinary tract, 3 separate components must be considered: a container for the urine, a passage for the urine to the surface and a system for maintaining continence. The tissues or materials used are shown in Table 1.

For the urine container (or pouch) we used most of the organs shown in the first column of Table 1 either alone or in combination. We believe there is little to choose between them, except that the more normal bladder that is included the better. Whatever is used, steps must be taken to make the container of adequate volume and of low intrinsic pressure.

This report is concerned only with the use of a narrow tube tunnelled into the urine container to provide a continent passage to the surface. The use of the appendix as a continent vesicostomy was first described by Mitrofanoff (1980) and developed by Duckett and Snyder (1985) but we have extended the theme and used all of the available narrow tubes (appendix, ureter and Fallopian tube) tunnelled into several types of container.

Patients and Methods

The technique has been used in 16 patients whose diagnoses are shown in Table 2: 12 were undergoing "undiversion" in the sense that an external appliance was to dispensed with, 2 were having an anterior pelvic exenteration for cancer and 2 were incontinent after extensive bladder outlet surgery.

The types of urine container are shown in Table

Table 1 Organs and Materials Used in Reconstruction of the Lower Urinary Tract

Pouch	*Outlet*	*Control*
Stomach	Ileum	Kock nipple
Ileum		± ileocaecal valve
Caecum	Appendix	
Colon	Fallopian tube	Mitrofanoff principle
Bladder	Ureter	
	Skin tube	Urethral or artificial sphincter
	Urethra	

Table 2 Diagnoses in 16 Patients in whom the Mitrofanoff Principle was Used

Diagnosis	*Number*
Exstrophy/epispadias	7
Multiple congenital anomalies	3
Spina bifida	2
Urethral sphincter incontinence	2
Bladder carcinoma	1
Cervical carcinoma	1

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

3. Where possible, the bowel of the existing conduit and any normal bladder were used. The patient whose pouch was made entirely of ileum had previously had a Kock pouch which was not continent. The narrow tubes that were used are shown in Table 4.

Method 1 (6 patients). The appendix and Fallopian tube were used in the same way. They were mobilised on their pedicles. The blind end of the appendix was removed (Fig. 1). One end was anastomosed to the pouch in a submucosal tunnel and the other end was brought to the surface as a stoma (Fig. 2).

The ureter was used in two ways.

Method 2 (6 patients). When a ureter had a long-standing anastomosis to a conduit (or Kock pouch) it was assumed that it would have an adequate blood supply from it. The viability of that supply was checked by putting a bulldog clamp on the ureter 6 cm from the conduit for 5 min and observing its colour. The ureter was then divided next to the bulldog clamp and about 4 cm were buried in the full thickness of the conduit wall (Fig. 3). The open end of the ureter was used as the stoma. The conduit was opened along its antimesenteric border and augmented with another segment of detubularised large bowel to form the pouch. The ureters draining the kidneys were anastomosed to the augmenting segment in a submucosal tunnel (Fig. 4).

Table 3 Pouches Used in 16 Patients with the Mitrofanoff Principle

Pouch	*Number*
Existing ileal conduit + colon	6
Colon alone	4
Bladder + ileum	2
Bladder + colon	1
Existing colon conduit + ileum	1
Ileum alone	1
Bladder alone	1

Table 4 Tubes Used for Continent Diversion Using the Mitrofanoff Principle

Tube	*Number*
Ureter	10
Appendix	5
Fallopian tube	1

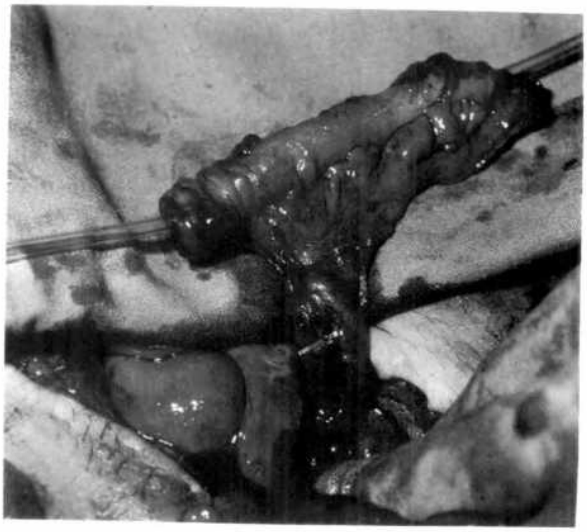

Fig. 1 Appendix mobilised on its mesentery. A catheter has been passed through its lumen.

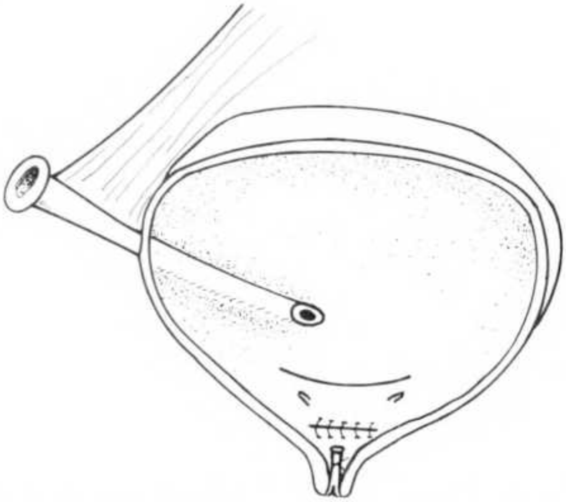

Fig. 2 Original type of Mitrofanoff. The appendix has been mobilised on its pedicle and tunnelled into the bladder wall. The bladder neck has been closed. The same technique would be used with a urine container formed from large bowel (Method 1).

Method 3 (4 patients). The other method with the ureter used its naturally occurring non-refluxing junction with the bladder. The absence of reflux was checked by cystography before the operation. In 3 patients the ureter was divided at an appropriate site above the bladder and brought out as the stoma. The upper end of this ureter was anastomosed as a trans-uretero-ureterostomy to the other side (Fig. 5). The bladder was augmented with

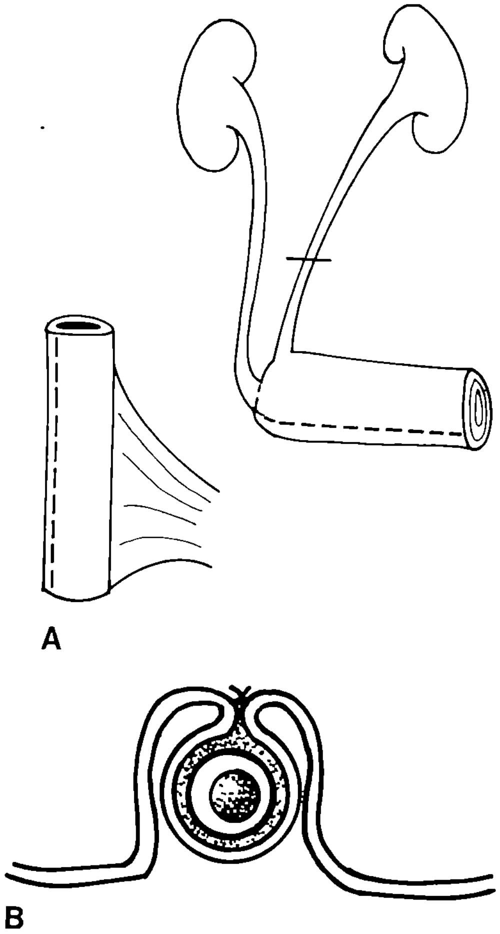

Fig. 3 Method 2. (A) the conduit has been mobilised The ureters are divided at the sites marked. The conduit is incised along its antimesenteric border A segment of large bowel has been isolated. (B) the stump of the right ureter has been buried in the full thickness of the conduit wall.

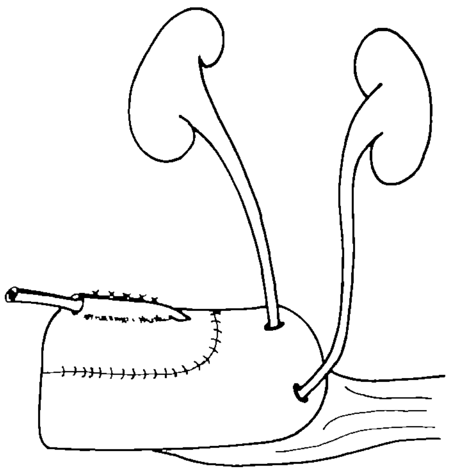

Fig. 4 Method 2 completed The conduit is augmented by the opened out large intestine The upper ureters are implanted into the urine container and the stump of the right ureter is ready to be made into a catheterisable conduit

bowel if necessary. In 1 patient who had a cutaneous ureterostomy, the remaining bladder had a stump of ureter suitable for a stoma; the upper ureter of her solitary kidney was tunnelled into the augmented bladder.

When the bladder was used, the bladder neck was closed. After one had re-opened, the method shown in Figure 6 was used. The urethra was divided below the bladder neck through the anterior wall of the vagina. It was then drawn up into the bladder, transfixed several times and buried under mucosa. Catheter drainage was maintained for 4 weeks.

Great care was taken in constructing the stoma so that self-catheterisation would be easy. The point at which the narrow tube emerged from the pouch was sutured to the peritoneal surface of the abdominal wall with black silk. The tube was brought to the surface as nearly in a straight line as possible. A long tongue of skin was mobilised and laid into the spatulated tube (Fig. 7); this allowed the stoma to be almost invisible (Fig. 8) and made a good funnel for catheterisation. The stoma was put as low as possible on the abdomen (certainly below the top of the pants) except in wheel-chair patients, in whom it was put close to the xiphisternum.

Results

Continence

Of 16 patients, 14 were completely continent and remain so at 4 to 36 months' follow-up.

One patient with a supposedly non-refluxing ureter that was used as a continent stoma (method 3) was dry until the pouch contained about 200 ml urine, when leakage began. The ureter was reimplanted and she is continent at 18 months' follow-up.

One patient with a buried ureter (method 2) is unpredictably incontinent and awaits revision.

Seven patients use a 12 F catheter, 6 a size 10 and one each sizes 8 and 6, for intermittent clean self-catheterisation.

Strictures

Two patients with the appendix as stoma (method 1) have developed strictures. One was at skin level and required a minor revision. The other was due

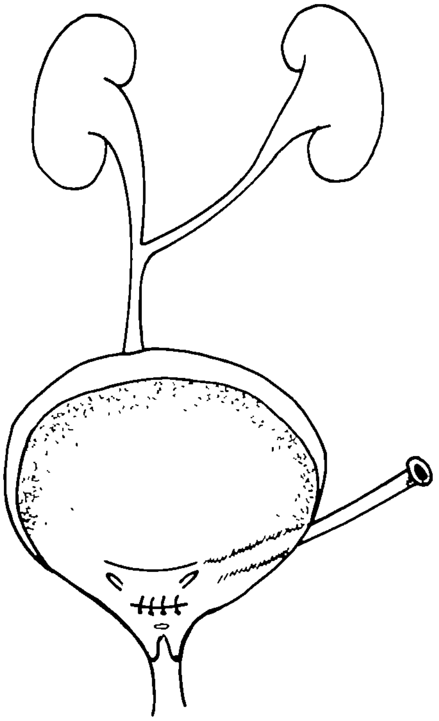

Fig. 5 Method 3. The left ureter has been divided and the lower stump used to make a catheterisable stoma A left to right trans-uretero-ureterostomy has been made The bladder neck has been closed.

to the raising of a false passage in mid-appendix while the patient was trying to catheterise in a dark lavatory after drinking several pints of beer. The stricture was opened longitudinally and closed transversely and it has remained open at 6 months' follow-up.

One patient whose lower ureter was used (method 3) had a rather rigid and narrow ureter which became progressively narrower until only a 5 F catheter could be passed. The narrowest parts were dilated to 12 F with a balloon positioned through a short ureteroscope. It re-stenosed but she is able to pass a 6 F catheter and empties the bladder with a syringe, which she finds acceptable.

Other complications

One patient had a small bowel to pouch fistula and another had a bladder neck fistula, both of which required surgical closure; 1 patient, aged 65 years, had severe post-operative pneumonia.

Discussion

The possibility of "getting rid of the bag" is discussed with all stoma patients attending the adolescent clinic at St Peter's Hospitals. The majority greet the prospect with alacrity but a few, usually those who are married with children and careers, do not see the need for such cosmetic surgery (Cumming *et al.*, 1988). We prefer to reconstruct the bladder, which is then emptied *per*

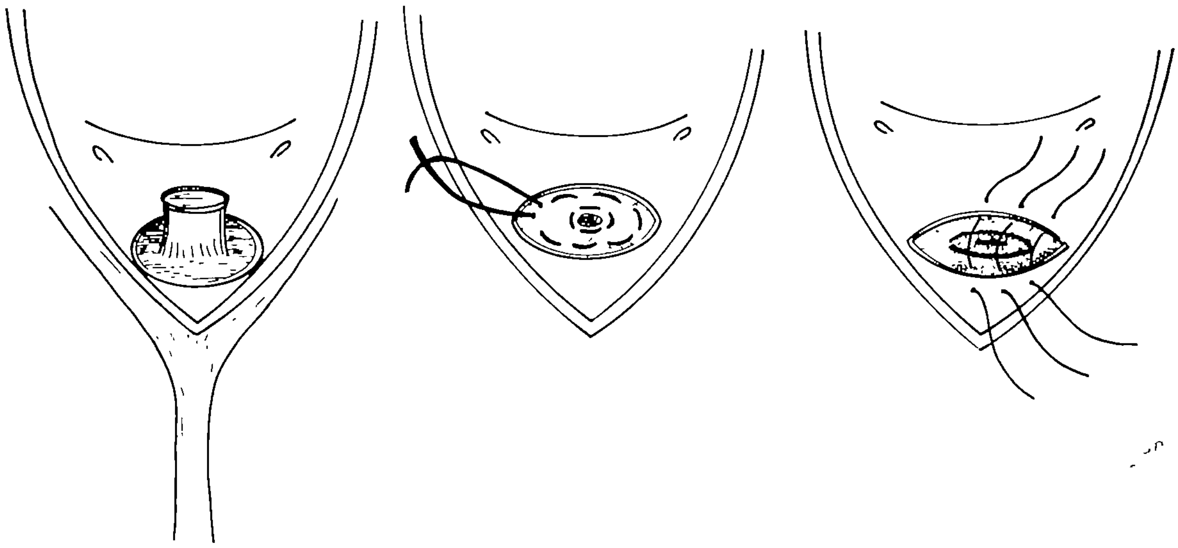

Fig. 6 Bladder neck closure. It is important to transect the urethra and invert it with several concentric sutures The bladder mucosa should be closed over the defect.

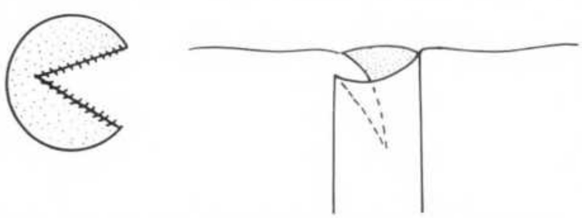

Fig. 7 Cutaneous anastomosis. A triangular flap of skin at least 2 cm long is mobilised and sutured into a spatulation of the conduit. If the conduit is short, a broader skin flap can be used to form a skin tube as a substitute.

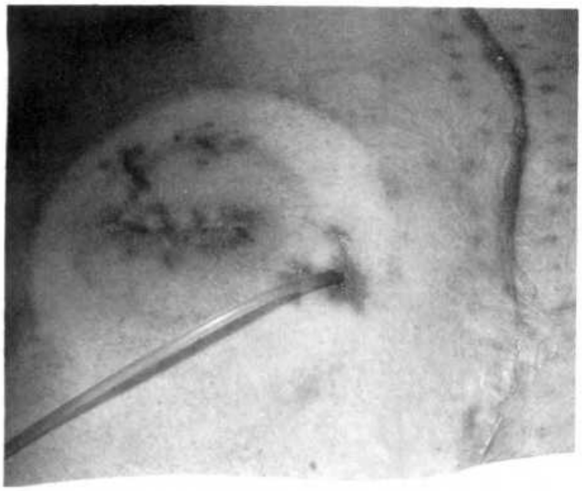

Fig. 8 Typical stoma with a catheter *in situ*. The shadow left by the old ileal stoma gives an indication of the scale.

urethram with or without intermittent self-catheterisation.

Continent suprapubic diversion is offered to patients with no usable bladder or urethra and to female patients who are wheelchair-bound and unable to catheterise the urethra.

Continent diversion is offered to patients with cancer in the pelvis only in carefully selected cases. They must be reasonably thin, relatively young, well motivated and have a reasonable prospect of cure; 3 of 7 patients refused when they heard the extent of additional surgery that was necessary; 1 of 4 who accepted had too little non-irradiated bowel for the procedure to be possible and 1 was inoperable. At present we do not believe that the additional surgery is justified in the elderly or infirm. Occasionally a patient may accept an offer of a Mitrofanoff, which has an acceptable complication rate, but decline a Kock pouch, which we have found difficult to construct (Cumming *et al.*, 1987).

Our experience in undiversion and continent internal diversions has been that any large hollow viscus can be made into a urine container. To keep the intrinsic pressure low we have used detubularised bowel and find that the maximum filling pressure is consistently less than 30 cm water.

For continent internal diversion we have found the narrow tube system of continence using appendix, ureter or Fallopian tube to be very satisfactory; 87% of patients were continent immediately. The method uses techniques, especially a tunnelled implantation, that are familiar to all urologists. The system is versatile and there are few patients in whom one method or another cannot be used.

Most of our patients were having surgery to rid themselves of an external appliance. As fewer children are diverted, this indication will largely disappear. The commonest use for this technique will be in patients with hopeless sphincter incontinence. After local reconstructive surgery (such as colposuspension in women) has failed on several occasions, an artifical urinary sphincter would be the treatment of choice. However, when such a device is not available or when the urethra is so damaged that it may not accept one, a catheterisable ureteric stoma (method 3) would be preferable to an ileal conduit.

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The Enigma of Interstitial Cystitis—an Autoimmune Disease?

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Summary—Interstitial cystitis (IC) is characterised by recurrent inflammation and destruction of bladder tissue without obvious cause. To determine whether this self-perpetuating disease is the result of an autoimmune disorder, we studied 26 patients with IC of mean duration 5 years and compared the results with those of a control group of similar age and sex with other urological complaints.

We performed a standard autoimmune profile and looked for specific antibodies to normal human bladder in the serum, using an indirect immunofluorescence technique. Deep bladder biopsies were examined by conventional histology and cryostat sections were studied with peroxidase-conjugated anti-human antibodies in a search for immunoglobulin deposition within the bladder.

Seventeen of 26 patients with IC (65%) and 5 of 14 controls (36%) demonstrated non-organ-specific antibodies; 40% of those with IC had anti-nuclear antibodies; 18 IC patients (75%) and 4 of 10 controls (40%) had anti-bladder antibodies present in the serum, but 5 healthy volunteers showed no such antibody activity. There was no statistically significant difference between the two groups for either type of antibody (Fisher's exact test). Only 5 of 17 patients with IC (29%) showed immunoglobulin deposition in the bladder epithelium, a similar proportion to controls (38%); 4 of these 5 had circulating anti-bladder antibodies present in the serum.

Although IC patients demonstrated a non-specific increase in antibody formation, this was not significantly different from a similar group of other urological patients. The lack of specificity makes this immunological response more likely to be a secondary phenomenon associated with inflammatory damage to the bladder rather than the primary cause of the disease.

Interstitial cystitis is one of the most disabling non-malignant disorders seen by the urologist. It is an uncommon disease whose hallmarks are a triad of irritative voiding symptoms, sterile cytologically negative urine and characteristic cystoscopic appearances.

Despite an awareness of the condition since the early 1900s (Nitze, 1907; Hunner, 1914), the cause of IC remains an enigma. Recurrent active inflammation and destruction of bladder tissue without obvious cause is suggestive of an autoimmune pathogenesis. Once initiated, such diseases tend to be self-perpetuating, with frequent exacerbations and remissions, and interstitial cystitis is no exception.

Much clinical and laboratory evidence has accumulated to support the hypothesis that IC is an immunologically mediated disease (Parivar and Bradbrook, 1986). Up to 90% of patients are middle-aged or elderly women, and in many there is a high incidence of other autoimmune diseases such as rheumatoid arthritis and Hashimoto's thyroiditis (Shipton, 1965; Silk, 1970). A history of drug hypersensitivity can be found in up to 70% of patients (Rosin *et al.*, 1979) and other atopic reactions are also more common (Oravisto *et al.*, 1970).

As with any autoimmune disease, there is an accumulation of lymphocytes and plasma cells

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within the bladder wall (Oravisto, 1980) and a high concentration of mast cells has also been described (Larsen *et al.*, 1982; Fall *et al.*, 1987). Mast cells produce vasoactive amines which are important in the development of allergic and anaphylactic reactions and capable of causing chronic inflammation and fibrosis when injected into animals (Silk, 1970; Kastrup *et al.* 1983). Anti-nuclear antibodies have been found in the serum of 54 to 85% of patients with IC (Jokinen *et al.*, 1972; Rosin *et al.*, 1979), while specific anti-bladder antibodies have been demonstrated in the serum of 45% of patients (Silk, 1970). Focal deposits of immunoglobulin, often associated with an inflammatory cell infiltration, have been reported both in bladder muscle (Gordon *et al.*, 1973) and blood vessel walls (Matilla, 1982), suggesting an immunological vasculitis. Furthermore, Matilla *et al.* (1983) found autoantibodies against elastin microfibrils and the typical vascular endothelial changes of other autoimmune disease (Linder and Lehto, 1978) in 70% of patients with IC.

In an attempt to clarify the autoimmune characteristics of IC, we studied 26 patients with the disease and compared their findings with those in a group of similar age and sex suffering from other urological problems.

Patients and Methods

Interstitial cystitis patients

The series comprised 24 women and 2 men with a mean age of 65 years (range 38–87) and an average duration of symptoms of 5 years (range 6 months–20 years). These patients presented with the typical clinical picture of IC in all degrees of severity. The diagnosis was based on a history of irritative voiding symptoms, intermittent or continuous suprapubic pain relieved by micturition and the classical cystoscopic signs of IC under general anaesthesia. Repeated urinary cultures were negative in all patients.

Controls

Thirteen women and 1 man with urological problems other than IC served as controls. Their mean age was 54 years (range 23–83). They all underwent cystoscopy for a number of conditions including recurrent urinary tract infection (6), bladder instability (3), irritative voiding symptoms following trauma (2), hypersensitive bladder, frequency following treated tuberculosis and psychological frequency; 4 patients had proven urinary tract infection at the time of investigation with more than 10^5 coliforms/ml of urine in each case.

Clinical evaluation

All patients were questioned regarding the nature and frequency of their symptoms, their past medical history and known allergies; 16 patients with IC and 10 control patients underwent intravenous urography, while 7 of the former group and 10 of the latter were submitted to full urodynamic assessment.

Cystoscopy and biopsy

All 40 patients were cystoscoped under general anaesthesia. The bladder was inspected under 70 cm of water pressure and when fluid ceased to enter it was drained and the capacity measured. Positive cystoscopic findings included ill-defined patches of erythema or "glomerulations" (Messing, 1985) which blanched or split during filling, ulceration, linear scars which occasionally radiated in a stellate fashion from a central bleeding area (the so-called Hunner's ulcer) and free or pinpoint petechial haemorrhage occurring either during the initial distension or after decompression and subsequent refilling.

Deep bladder biopsies including muscle were taken by cold cup biopsy. The tissue was fixed in formalin for routine histological examination using haematoxylin and eosin stains as well as toluidine blue stain for mast cells. All specimens were reviewed by the same member of the pathology department. The correlation between the duration of symptoms and the presence of bladder fibrosis was analysed by the Mann-Whitney U test.

Immunological studies

Serum samples stored frozen at −20°C from all patients were tested for auto-antibodies to nuclei, smooth muscle, thyroid microsome and colloid, mitochondria, parietal cells and reticulin by a standard indirect immunofluorescence technique.

The sera were also examined for evidence of circulating antibodies binding specifically to bladder, again using indirect immunofluorescence. For this test 4 micron cryostat sections of bladder from blood group 0 patients, snap frozen whilst fresh, were used as the antigenic substrate. Serum specimens were tested neat and diluted 1/10. Fluorescein-conjugated polyvalent anti-human IgG and IgM (Daco) were used at dilutions predetermined by chess board titration to detect immunoglobulin binding to the substrate. Non-specific binding was excluded by the inclusion of negative sera from healthy volunteers and a buffer control in each batch of tests.

Evidence of organ-specific anti-bladder antibodies was sought in the fixed bladder biopsies obtained at the original cystoscopy. Polyvalent anti-human 1gG, 1gA, 1gM, 1gD and 1gE were each incubated with these specimens of bladder tissue in an attempt to demonstrate the presence of fixed specific anti-bladder antibodies using an indirect immunoperoxidase method following trypsin digestion, which increases the sensitivity of detection of immunoglobulins in tissue sections (MacIver and Mepham, 1982).

Results

Clinical evaluation

All but 2 patients with IC complained of urinary frequency by day, while only 2 others were spared nocturnal frequency (Table 1); 18 of the 26 (70%) suffered a degree of urgency, 15 (58%) experienced suprapubic pain which was relieved by micturition and 13 (50%) complained of dysuria. By contrast, haematuria was rare, with only 4 patients ever being troubled by it.

Symptoms in the control patients tended to be less specific, probably due to the heterogeneous nature of the group. While frequency and urgency were common complaints, nocturia and dysuria were less so and bladder pain and haematuria were rare.

Of note in the past medical history of those with IC, 3 had rheumatoid arthritis and one had Hashimoto's thyroiditis. Specific allergies were infrequent; 2 patients were allergic to penicillin and one was sensitive to nickel. Another subsequently proved to be allergic to dimethyl sulfoxide, a product with anti-inflammatory properties used in the treatment of IC.

Intravenous urography was unhelpful in the diagnosis of IC. Of the 16 who underwent this investigation no abnormality was demonstrated in 10, while 6 patients were thought to have reduced bladder capacity. Urodynamic investigations were similarly of little benefit, with the majority of those studied showing a small capacity hypersensitive bladder.

Table 1 Symptoms

	Interstitial cystitis (*n*=26) (%)	*Control group* (*n*=14) (%)
Frequency	24 (92)	12 (86)
Nocturia	24 (92)	5 (36)
Dysuria	13 (50)	3 (21)
Urgency	18 (70)	10 (71)
Haematuria	4 (15)	1 (7)
Bladder pain	15 (58)	1 (7)

Cystoscopy

In each case the bladder initially had a typical appearance with ill-defined patches of reddened mucosa and small vessels radiating to a central scar. A true Hunner's ulcer was seen in only 6 patients. Following distension and subsequent decompression, all but 6 cases (77%) showed petechial oozing of blood from the mucosa, while in 18 (69%) bleeding fissures could be seen throughout the bladder.

The mean bladder capacity under general anaesthesia in patients with IC was 302 ml (range 100–600) and showed a statistical correlation with the duration of symptoms ($r=0.42$, $P<0.05$). In the control group the mean bladder capacity was 351 ml (range 190–600).

Histology

The bladder biopsies all showed characteristic histological features in those patients with IC, albeit of varying degree (Table 2). Thus in 19 (73%) the mucosa was ulcerated and in a further 3 patients inflammatory cells were infiltrating the epithelium. Only 4 patients had a normal mucosa. Squamous metaplasia was identified in 1 patient. Submucosal oedema was a prominent feature in only 5 biopsies (20%) and dilated thin-walled blood vessels were seen in 8 (31%).

An inflammatory cell infiltrate of variable density was present in each case and generally extended throughout the entire biopsy. Lymphocytes were the dominant cell in 18 cases (69%) but neutrophil polymorphs were also present in 17 (65%) and

Table 2 Histology

	Interstitial cystitis (*n*=26) (%)	*Control group* (*n*=14) (%)
Mucosa		
Normal	4 (15)	9 (65)
Inflamed	3	2
Ulcerated	19 (73)	3
Submucosal oedema	5 (20)	3 (21)
Vascular dilatation	8 (31)	1 (7)
Cellular infiltrate		
Polymorphs	17 (65)	5 (35)
Lymphocytes	23 (88)	5 (35)
Macrophages	24 (92)	5 (35)
Fibrosis	14 (54)	2 (14)

macrophages in 24 (92%). Although scattered mast cells were present, we were unable to confirm the findings of Kastrup *et al.* (1983), who found 20 such cells per sq mm in the muscle wall. Stromal fibrosis was apparent in 14 biopsies (54%) and was prominent in half of these cases. The longer the duration of symptoms, the greater was the likelihood of fibrosis being present in the bladder ($P = 0.027$).

The histological abnormalities in the control group were less impressive: 3 patients with recurrent urinary tract infection and proven infection at the time of investigation had an ulcerated (2) or inflamed (1) mucosa. They each had a prominent inflammatory cell infiltrate with polymorphs, lymphocytes and macrophages, while 2 also had significant stromal fibrosis. In 1 patient with a hypersensitive bladder, histology showed an ulcerated epithelium, submucosal oedema and a lymphocyte infiltration, while a lady with previous urinary tract tuberculosis had submucosal oedema and a predominance of lymphocytes in her bladder biopsy. In the remaining cases the biopsies were within normal limits.

Auto-immune profile

Anti-nuclear antibodies were present in titres of less than 1/80 in 10 of 26 patients with IC (40%) and in 4 of 14 control patients (29%) (Table 3). These antibodies most commonly (75%) gave a homogeneous pattern of fluorescence in both groups. Only 2 individuals with IC and 1 control had anti-nuclear antibodies in a titre of 1/80 or more.

Five patients with IC had anti-thyroid antibodies, including 1 lady with Hashimoto's thyroiditis, and 2 each had smooth muscle, mitochondrial or parietal cell antibodies, all at significant titre.

Overall, 17 of 26 patients with IC (65%) had some evidence of auto-antibody formation, while 5 of 14 control patients (36%) showed the same phenomenon.

Table 3 Auto-immune Profile

	Interstitial cystitis (*n*=26)	*Control group* (*n*=14)
Antinuclear antibody	12 (46%)	4 (29%)
<1/80	10	3
1/80 or greater	2	1
Smooth muscle antibody	2	1
Thyroid		
Microsome antibody	5	0
Colloid antibody	1	0
Mitochrondial antibody	2	0
Parietal cell antibody	2	0
Reticulin antibody	0	2

Serum anti-bladder antibodies

Bladder-specific IgG antibodies were present in the serum of 18 of 24 patients with IC (75%) and 4 of 10 control patients (40%), while similar IgM antibodies were detected in 63 and 30% respectively (Table 4). Sera from normal volunteers without urological disorders did not contain anti-bladder antibodies. Serum samples from 4 patients with symptoms of IC for 1 to 12 years were tested sequentially at up to 3-monthly intervals for 1 year. In no case did the result of the test change with time.

Fixed bladder antibodies

Using an indirect immunoperoxidase technique with anti-IgG, 3 of 17 patients (18%) with IC in whom mucosa was available for assessment showed immunoglobulin deposition in the surface epithelium of the bladder, presumably representing anti-bladder antibodies, while 5 (29%) revealed immunoglobulin deposition when anti-IgA was employed (Table 5). The figures for the control group were 4

Table 4 Serum Anti-bladder Antibodies

	Interstitial cystitis (*n*=24) (%)	*Control group* (*n*=10) (%)
Using fluorescent-conjugated anti-IgG	18 (75)	4 (40)
Using fluorescent-conjugated anti-IgM	15 (63)	3 (30)

Table 5 Fixed Anti-bladder Antibodies

	Interstitial cystitis (*n*=25)	*Control group* (*n*=10)
IgG		
Surface epithelium	3/17 (18%)	4/8 (50%)
Plasma cells and macrophages	17	1
Blood vessel walls	4	1
IgA		
Surface epithelium	5/17 (29%)	3/8 (38%)
Plasma cells and macrophages	21	1
Blood vessel walls	3	0
IgM		
Surface epithelium	0/17	0/8
Plasma cells and macrophages	10	0
Blood vessel walls	12	4

of 8 (50%) and 3 of 8 (38%) respectively. Of the 5 patients with IC who had 1gA in the bladder wall, 4 had anti-bladder antibodies in the serum. As expected, significant amounts of immunoglobulin were apparent in plasma cells and macrophages, whilst deposits of 1gM in blood vessel walls were most likely to be secondary to the inflammatory reaction and occurred in both IC patients and controls.

Anti-1gM, 1gD and 1gE antibodies did not show any immunoglobulin deposition in the bladder epithelium.

Discussion

Autoimmune disorders are caused by antibodies and immunologically competent cells active against components of the body. In organ-specific diseases such as Hashimoto's thyroiditis, specific antibodies are produced which together with lymphocyte and plasma cell infiltration result in structural and functional damage. Non-organ-specific autoimmune diseases like systemic lupus erythematosus are characterised by antibodies which cause wide and varied tissue destruction. Between these two there is a group of diseases in which the antibodies are non-organ-specific but the immunologically mediated damage is confined to one organ (Turner Warwick and Doniach, 1965; Roitt and Doniach, 1969).

The possibility that IC is an auto-immune disease has long been considered (Messing, 1985). Following bladder injury from a variety of causes there is cellular destruction and release or alteration of antigen which induces antibody production. This in turn causes more bladder damage. Alternatively, normal bladder, or even some non-bladder antigen, may initiate antibody production through an inappropriate immune response and the antibody then causes the primary injury.

Our results lend little support to this concept of IC being an autoimmune disease. We have found no increased incidence of associated autoimmune diseases, no history of atopy or drug hypersensitivity, and the histological appearances of the bladder were not specific.

Some of the most supportive evidence that IC is an auto-immune disease was provided by Jokinen *et al.* (1972), who found anti-nuclear antibodies in the serum of 85% of patients with the condition. We found this to be the case in only 46%, while 29% of the control group had a similar result. Furthermore, in only 2 patients were anti-nuclear antibodies present at a titre likely to be of significance (1/80 or more). Since less than half of those studied had a positive result, estimation of anti-nuclear antibody cannot be relied on as a diagnostic test for IC, and with only 4% having a significant amount of antibody it cannot be considered important as a cause of the disease. These results, and the low incidence of other non-organ-specific antibodies in patients with IC, probably represent a normal distribution in patients with inflammatory disease.

Although specific anti-bladder antibodies were found in the serum of patients with IC in up to 75% of cases, they were also present in 40% of controls. There was no correlation between the duration of symptoms and the presence of antibodies in the former group to suggest that we were merely studying end-stage disease after the autoimmune process had burnt itself out. The anti-bladder antibodies found in the control group reflect a lack of specificity for IC and indeed, analysis of the data by Fisher's exact probability test revealed no significant difference between the presence of these antibodies in patients and controls.

Finally, we found fixed immunoglobulins in the bladder wall in only 29% of patients with IC, while up to 50% of patients with other bladder diseases had similar immunoglobulin deposition. We were therefore unable to confirm the observations of Gordon *et al.* (1973) who, using direct immunofluorescence, showed a difference in antibody deposition between those with IC and control patients.

Our results tend to confirm the limited experimental research into the cause of IC. In 1970, Silk was unable to produce gross or microscopic evidence of the disease in rabbits by immunisation with bladder incorporated into Freund's complete adjuvant and to date there is no suitable animal model for the disease. Furthermore, if an autoimmune response directed against bladder tissue were responsible for the disease, the relief of all symptoms following urinary diversion without cystectomy would not be expected (Messing and Stamey 1978), and neither would the recurrence of IC-like lesions in the intestinal segments of patients who have undergone augmentation cystoplasty (McGuire *et al.*, 1973; Messing and Stamey, 1978).

Since the immunological changes we have found are not specific for IC, it is probable that they represent response to tissue damage due to some other mechanism, and are a secondary phenomenon rather than a primary cause of the disease. The detection of antibodies, both in the serum and in bladder biopsies from patients with IC, probably means we are measuring a degree of injury to the bladder. A similar development of autoantibodies to epithelium occurs following burns to the skin (Ablin *et al.*, 1969). Whatever causes IC therefore produces a chronic inflammatory state with a mixed cellular infiltrate of macrophages and plasma cells, many of which contain IgA as would be expected (Kirkham *et al.*, 1983). We would speculate that this in turn is responsible for the subsequent damage to the bladder and activation of the immune system in a manner analogous to inflammatory changes elsewhere in the body.

It is of note that the duration of symptoms of IC correlates with the degree of bladder wall fibrosis ($P = 0.027$) and also with the anatomical bladder capacity under general anaesthesia ($P < 0.05$). Whatever the cause of IC, this suggests that its effects are progressive in nature and culminate in the same end-point of all chronic inflammatory conditions, namely fibrosis.

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Concurrent Adriamycin and Radiotherapy in Locally Advanced Bladder Cancer

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Summary—A prospective 2-phase study was performed on 24 patients with locally advanced transitional cell carcinoma of the urinary bladder to evaluate the toxicity of integrated treatment with Adriamycin 10 mg/m^2 (group A) or 20 mg/m^2 (group B) and hyperfractionated, accelerated radiotherapy. Local and systemic toxicity with Adriamycin 10 mg/m^2 was significantly lower than with 20 mg/m^2. Complete tumour remission was achieved in 18 patients (6 of 8 patients in group A and 12 of 16 in group B). In 12 cases the treatment could be stopped after the first series.

Radical cystectomy with or without pre-operative radiotherapy is generally considered the best treatment with regard to local tumour control and survival (Martur *et al.*, 1981; Whitmore, 1983; Montie *et al.*, 1984). The 5-year survival rate for patients with T3 tumours varies from 35 to 50% (van der Werf-Messing, 1975; Prout, 1976; Whitmore *et al.*, 1977). Approximately 40% of patients die from metastatic disease; local recurrence has been noted in about 15% (Whitmore, 1983; Hohenfellner and Jacobi, 1984). Considering the cancer-related death rate, the early and late morbidity of urinary diversion, loss of potency and the operative mortality rate of 7% (higher in less experienced institutions), these results are far from satisfactory.

As an alternative to radical cystectomy, definitive radiotherapy offers the advantage of bladder conservation and avoidance of the above side effects in those patients who achieve complete resolution of local tumour. However, the complete remission rate in T3 and T4 bladder cancer is only 42 and 6% respectively (Hope-Stone *et al.*, 1981). Patients with complete remission have a 5-year survival rate of 56% (Blandy *et al.*, 1980). These results compare favourably with the results of cystectomy (Bloom *et al.*, 1982).

If tumour eradication combined with organ conservation is one of our major goals, it is reasonable to apply techniques which significantly increase the local control rate of irradiation and thus lead to an increase in survival.

Recent reports have indicated that an integrated therapy consisting of systemic chemotherapy and definitive radiotherapy applied concurrently yields a local control rate of approximately 70% in locally advanced transitional cell carcinoma of the urinary bladder (Shipley *et al.*, 1984; Jakse *et al.*, 1985).

Adriamycin gives an overall response rate of 19% in metastatic urothelial cancer (Loening, 1984). This agent forms part of several effective chemotherapy protocols and there is good evidence that it enhances the effects of irradiation (Durand, 1976; Bistrovic *et al.*, 1978; Teicher *et al.*, 1981). Dollinger *et al.* (1979) reported complete remission in 5 of 6 patients with bladder cancer treated with Adriamycin 20 mg/m^2 weekly and concomitant definitive radiotherapy. Based on this evidence and our experience with radiotherapy and concurrent cisplatin, we have used a protocol of weekly Adriamycin and concurrent radiotherapy in locally advanced bladder cancer.

Patients and Methods

Patients were selected for these protocols according to one of the following criteria: (1) serum creatinine >1.5 mg%, (2) poor performance status (WHO grade 2), (3) refusal of intensive chemotherapy such as cisplatin.

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From March 1984 to May 1987, 24 patients (20 male, 4 female) with biopsy-proven invasive transitional cell carcinoma were treated with radiotherapy and concurrent Adriamycin. The patients' characteristics are given in Table 1. All patients had a WHO performance status of 0 to 2. The tumour was confined to the true pelvis on initial presentation.

Technique

The initial evaluation included a history and physical examination, complete laboratory diagnostic studies, intravenous urography, chest X-ray and bone scan. Lymph node and liver involvement was investigated by CT scan. The local tumour extent was estimated by (1) bimanual examination under anaesthesia, percutaneous sonography and/or CT, and (2) transurethral resection with a separate biopsy of the tumour base. The tumour stage and grade are presented in Table 1.

Therapy

TUR was followed by a combined chemotherapy-radiotherapy regimen after an interval of 4 weeks. Adriamycin was administered 2 h before the first irradiation and then given weekly 4 or 6 times. The dosage was initially 10 mg/m^2 (8 patients) and was increased to 20 mg/m^2 in the subsequent 16 patients. Irradiation treatment was given in 2 daily fractions of 1.6 Gy on 3 consecutive days of the week for 4 weeks (total dosage: 38.4 Gy). The irradiation was delivered on 2 opposite portals extended up to L5 and laterally to the acetabulum, and was limited caudally by the lower rim of the pubic bone in the first series. After re-evaluation the irradiation was continued to a total dosage of 57.6 Gy. The irradiation portals were confined to the bladder in the second series. There was an interval of 4 weeks between both series.

Table 1 Details of Patients (n = 24)

	No of patients
Sex	
Female	4
Male	20
Tumour stage	
T2	4
T3	20
Tumour grade	
III	9
IV	15
Upper urinary tract obstruction	10*

*2 patients had bilateral hydronephrosis

Evaluation of toxicity

Stool and voiding frequency, complete blood count and body weight were monitored throughout therapy and thereafter every 3 months.

Evaluation of tumour response

Two weeks after the first series the local response was evaluated by TUR of the tumour area, bimanual palpation and CT scan. In the case of a histologically confirmed complete response, treatment was stopped. The second evaluation was performed 2 to 4 weeks after termination of the second series.

Results

Tumour response

The local response of the primary tumour evaluated by TUR and CT scan in all patients is given in Table 2. A complete response was achieved in 18 (75%) of the 24 patients, in 13 of them after the first series of integrated therapy. Follow-up ranged from 6 to 41 months (average 17). Tumour recurrence (pT2, grade 3) was noted in 1 patient 7 months after termination of treatment. He refused further treatment.

In 5 patients metastases were detected in the liver (n = 2), bone (n = 1), lymph nodes (n = 3) and the peritoneal cavity (n = 1); 10 patients died. The causes of death and the local response are shown in Table 3. The fate of 2 patients is unknown.

Patient compliance

All but 3 patients completed the treatment. In these patients it was stopped because of grade 3 diarrhoea

Table 2 Local Tumour Response

	Complete response	*Persistent disease*
10 mg/m^2 (n = 8)		
First series	3	5
Second series	3	2
20 mg/m^2 (n = 16)		
First series	10	6
Second series	2	4

Table 3 Cause of Death in Relation to Local Tumour Response

	Complete response	*Persistent disease*
Metastases	3	2
Unrelated	2	—
Local disease	—	3

after receiving 28 Gy and 20 mg/m^2 Adriamycin weekly.

Toxicity

The data on acute toxicity are shown in Table 4. Haematological toxicity was mild in all patients. The leucocyte count decreased in 17 patients, but fell below 3500 (3100, 3400, 3300, 2800, 3100) in only 5 cases; 13 patients experienced mild to moderate alopecia. A decrease in haemoglobin values ranging from 1 to 2.2% was noted in 4 patients, all of whom received 20 mg/m^2 Adriamycin. Diarrhoea was the main problem. In 3 patients treatment had to be stopped and in 1 patient there was a break for 1 week; 2 patients needed supportive treatment after termination of the first series. A reduction in body weight was observed in 15 cases. The mean weight loss was 2.8 kg (range 1–5). Chronic toxicity was noted in 4 patients (Table 4), the most severe being a vesico-intestinal fistula in a patient with local tumour progression, shrunken bladder and proctitis.

Table 4 Acute and Chronic Toxicity

	10 mg/m^2	*20 mg/m^2*
Acute toxicity		
Leucopenia	2	3
Decrease in leucocytes*	2	10
Decrease in haemoglobin†	—	4
Alopecia grade 1	3	6
Alopecia grade 2	2	3
Diarrhoea grade 2	2	5
Diarrhoea grade 3	2	4
Chronic toxicity		
Proctitis	2	2
Decreased bladder capacity	1	2
Vesico-intestinal fistula	—	1

*Decrease >2000 from the initial value.
†Decrease >1 g/% from the initial value.

Discussion

Multimodality treatment regimens including systemic chemotherapy have been introduced only recently in bladder cancer therapy. Hall *et al.* (1984) performed "radical" TUR and administered a high dose of methotrexate. They reported a 58% complete response rate and 42% of these patients remained tumour-free for at least 2 years. Lundbeck and Christophersen (1979) treated patients with locally advanced bladder cancer with concurrent radiotherapy and chemotherapy and achieved complete tumour remission in 14 of 18 patients. We used a similar approach (Jakse *et al.*, 1985) and Shipley *et al.* (1984) administered a single agent and definitive irradiation. Both studies gave almost identical results and provide evidence that cisplatin enhances the efficacy of radiotherapy in terms of local tumour control. In a recent study we included Adriamycin 10 mg/m^2 (weekly) in the combined treatment (Jakse *et al.*, 1987) and also changed the radiotherapy protocol. The rationale for these changes was that hyperfractionated split course irradiation has the theoretical advantage of decreasing the injury to normal tissue, reduces the chance of tumour repopulation by rapidly dividing cells and also reduces the number of treatment days by delivering conventional radiation doses per fraction 2 to 3 times a day (Richie *et al.*, 1981; Thames *et al.*, 1983). Preliminary results showed that this protocol was effective and did not increase local toxicity (Jakse *et al.*, 1987).

Several important findings have evolved from this study. Adriamycin 10 mg/m^2 given in a weekly schedule 4 to 6 times provides an acceptable degree of acute toxicity and can be delivered safely in patients with WHO performance status grade 2. An increase in the dosage of Adriamycin to 20 mg/m^2 also increases the percentage of acute as well as chronic toxicity. The rest period of 4 days between the treatment days is not only preferred by the patients, but is also of importance with regard to hospital costs in those instances where the treatment can be given on an out-patient basis. The complete remission rate is higher than that reported with radiotherapy alone and comparable with that reported earlier using cisplatin (Shipley *et al.*, 1984; Jakse *et al.*, 1985).

An early evaluation of the results of treatment (after ≈40 Gy) is beneficial, since a significant proportion of patients experienced complete tumour remission after the first series. The occurrence of distant metastases seems to be unaffected by Adriamycin mono-therapy.

At the present time there are several treatment options in addition to radical cystectomy which can be offered to the patient with locally advanced bladder cancer. One of these options is concurrent radiotherapy and chemotherapy. There is good evidence that the addition of drugs such as cisplatin, 5-FU or Adriamycin will give good results in patients who are not fit for cystectomy or who refuse cystectomy as initial treatment (Shipley *et al.*, 1984; Rotman *et al.*, 1987). Low dose Adriamycin seems to be useful in patients with a poor performance status and increased serum creatinine levels, since systemic toxicity is extremely low and local toxicity does not exceed that reported for conventional radiotherapy (Goffinet *et al.*, 1975). Moreover, the complete remission rate for T3 bladder cancer is surprisingly good.

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New Combination Chemotherapy Programme for Bladder Cancer

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Summary—Forty patients with either metastatic, post-radiotherapy recurrent, or poor prognosis locally advanced transitional cell carcinoma of the bladder were treated in a new combination chemotherapy programme with methotrexate, vinblastine, mitozantrone and JM8 (carboplatin); 33 patients were assessable for response. There were 9 complete responses (27%), 12 partial responses (36%) and 7 disease stabilisations (21%); 5 patients (15%) had progressive disease. The median duration of complete response has not been reached and is in excess of 9 months (range 4–> 18 months). This regimen was without significant toxicity and this is in contrast with M-VAC, which is thought to be currently the most effective treatment for urothelial cancer.

Patients with metastatic or post-radiation recurrent invasive bladder cancer have a limited prospect of survival. Cytotoxic chemotherapy using single agents such as methotrexate and cisplatin produces responses in approximately 30 to 40% of patients but less than 5% are alive 1 year from presentation. There has been interest recently in multiple agent chemotherapy programmes and amongst the most effective regimens investigated are CMV, developed by the Stanford Group, and M-VAC, pioneered at the Memorial Sloan-Kettering Hospital. Of these two programmes M-VAC is the more successful and Sternberg *et al.* (1988) reported a 25% complete response rate and 31% partial response rate in 83 patients treated for metastatic disease. An additional 12% of patients were converted into complete responders following surgical resection. Ten of 45 patients (22%) with transitional cell cancer confined to the bladder responded to M-VAC given as primary therapy (Scher *et al.*, 1988). The toxicity of this combination is significant: 20% of patients required hospital admission with significant neutropenic sepsis, 31% had grade 1 renal toxicity and 41% grade 1 mucositis. Vomiting was universal, all patients had complete alopecia and there were 4% treatment-related deaths. Although many centres have been unable to reproduce the responses reported by the New York group, there is no doubt that this regimen is the most effective programme available today for the treatment of transitional cell carcinoma of the bladder. We have designed an alternate programme in an attempt to reproduce the same response without the same order of side effects. We report the early results of treatment with combination chemotherapy using methotrexate, vinblastine, mitozantrone and JM8 (carboplatin).

Patients and Methods

Forty patients with transitional cell carcinoma of the bladder were entered into treatment; 35 have completed chemotherapy and are included in this analysis; 21 men and 14 women with a median age of 67 years (range 39–78) were treated. Thirteen patients had bulky, locally advanced, previously untreated tumours (>T3b), 10 had post-radiation recurrent locally invasive disease and 12 had metastatic bladder cancer. Three patients had histological grade 1, 6 patients grade 2, 24 grade 3 and 2 grade x tumours. All had significant symptoms relating to their disease.

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

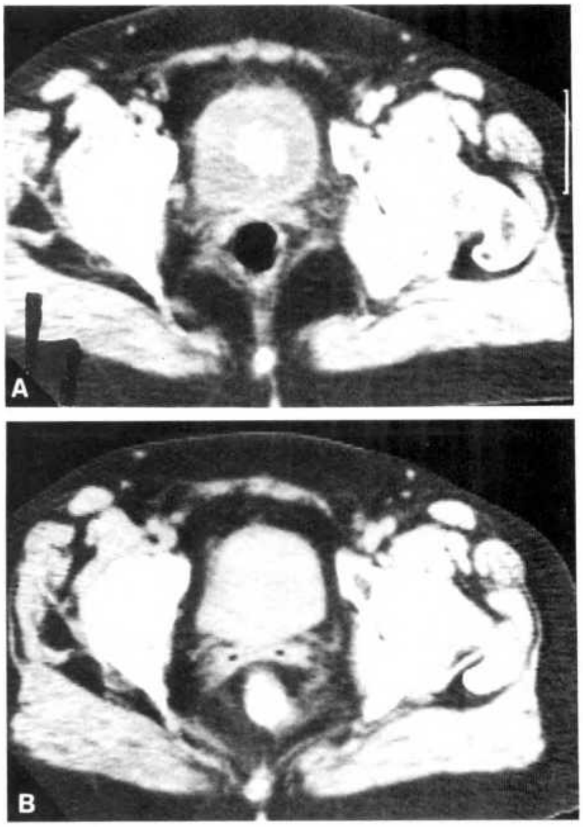

Fig. 1 Response of T4 bladder tumour to MVMJ. (A) Before treatment. (B) After treatment.

which was controlled with dexamethasone and lorazepam. Grade 1 alopecia developed in 14 patients and grade 2 in 4; 25 patients required transfusion of red cells and 5 of this group required platelets. In 7 patients grade 1 oral ulceration was seen and 2 patients had grade 2 oral ulceration; 10 patients were admitted with fever which in 9 was associated with neutropenia. In no neutropenic patient was a source of infection identified or an organism cultured. White cell and platelet nadirs are described in Figures 3 and 4. Mean serum creatinine before treatment was 199(SD 42) nmol/l and after treatment 104(SD 33) nmol/l.

Discussion

The early results of treatment with MVMJ, a new combination chemotherapy programme for transitional cell carcinoma of the bladder, are reported. Of 33 patients, 21 (63%) had a complete or partial response and 7 (21%) disease stabilisation. The median duration of complete and partial response

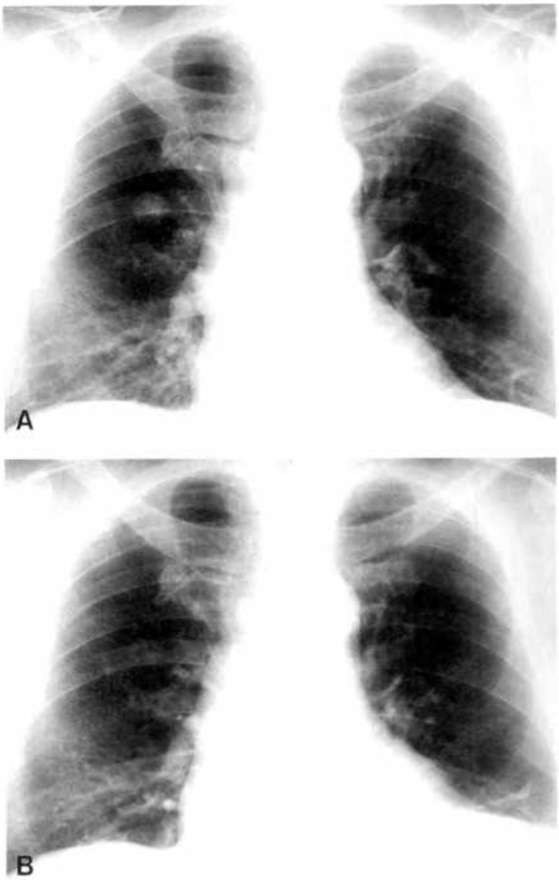

Fig. 2 Response of pulmonary metastasis to MVMJ. (A) Before treatment. (B) After treatment.

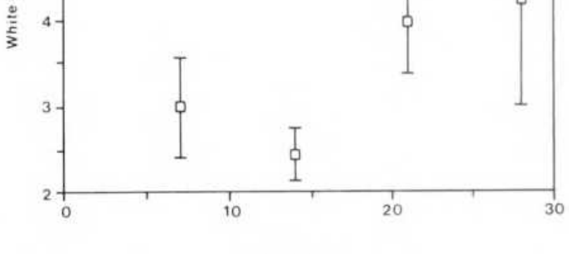

Fig. 3 White cell count (95% confidence intervals).

All patients were staged by means of clinical examination, routine haematology and biochemistry, chest X-ray, bone scan, CT scan of the pelvis and abdomen, and cystoscopy with cystoscopic resection biopsy. Treatment consisted of methotrexate 50 mg/m^2, vinblastine 3 mg/m^3, mitozantrone 10 mg/m^2, and JM8 200 mg/m^2 on day 1 with methotrexate 50 mg/m^2 on day 15 of a 28-day treatment cycle. Folinic acid 15 mg orally was given 24 h after administration of methotrexate. Mitozantrone was given by intravenous injection over 30 min in 100 ml of 5% dextrose followed by JM8 in 250 ml of 5% dextrose over 30 min. Vinblastine and methotrexate were given by bolus injection. When the serum creatinine was in the range 120 to 180 nmol/l, half-dosage methotrexate and JM8 were given. The dosages of JM8 and mitozantrone were altered according to white cell and platelet nadirs. Dosages were increased by 20% if the WBC nadir was $> 2.5 \times 10^9$/l and the platelet nadir $> 75 \times 10^9$/l; treatment dosages were unchanged when the white count nadir was between 1.5 and 2.5×10^9/l with a platelet nadir of 50 to 5×10^9/l. Dosages were decreased by 20% when the white count nadir was $< 1.5 \times 10^9$/l or the platelet count fell below 50×10^9/l. All patients received a minimum of 2 cycles of treatment unless major clinical deterioration developed.

Treatment was stopped after 4 cycles unless there was evidence of continuing, but still incomplete response. Patients were excluded from this treatment programme if they had serum creatinine concentrations > 180 nmol/l, secondary to obstructive uropathy, which failed to improve with insertion of nephrostomy tubes. There was no exclusion on the basis of age or performance status. Complete response was described on either a pathological or a clinical basis. Pathological response was defined as histological evidence of elimination of disease by multiple cystoscopic biopsy, while clinical response included response as assessed radiologically and by physical examination. Partial response indicated $> 50\%$ tumour regression, stable disease $< 50\%$ tumour regression and progressive disease $> 25\%$ increase in measurable tumour parameters. Toxicity was defined according to WHO criteria.

Results

Nine patients (27%) had a complete response which was pathologically confirmed in 5; 12 patients (36%) had a partial response, 7 (21%) had disease stabilisation and 4 had progressive disease. There were 2 deaths within the first 5 days of treatment, 1 from a pulmonary embolus and another from progressive disease. The median duration of response of the complete responders has not yet been reached and is in excess of 9 months (range 4–18+). The median duration of survival has not been reached and is in excess of 12 months (range 7–18+). The median duration of partial response has not been reached and is in excess of 6 months (range 2–14+) and the median duration of survival of partial responders has not been reached and is in excess of 6 months (range 2–16+). The median duration of survival for those patients achieving disease stabilisation was 6 months (range 2–17+) with a median duration of survival of 7 months (range 4–14+) (Table 1).

Assessing response in terms of the disease site, 8 of 22 patients (36%) with locally advanced disease had a complete response (5 pathological and 3 clinical complete response). Six patients had a partial response, with disease downstaging to clinical stage T0 but pathological evidence of microscopic invasive disease; 3 of 10 patients with locally advanced disease previously treated by radiotherapy had a complete response (2 pathological and 1 clinical). Of those patients with metastatic cancer, 1 patient with nodal disease had a complete response, 6 had partial responses and 3 had disease stabilisation (Table 2). Figures 1 and 2 describe responses in patients with locally advanced and metastatic tumours.

There was very little acute toxicity, with only 3 patients having WHO grade 2 or more vomiting

Table 1 Response and Survival

Response (%)		*Duration of response (months) Median (range)*	*Duration of survival (weeks) Median (range)*
Complete	9 (27)	>9 (4–18+)	>12 (7–18+)
Partial	12 (36)	>6 (2–14+)	>6 (2–16+)
Stable	7 (21)	6 (2–17+)	7 (4–17+)

Table 2 Response versus Site

	PCR	*CCR*	*PR*	*SD*	*PD*	*ED*
Locally advanced						
Untreated	3	2	6		1	1
Previous radiotherapy	2	1		4	3	
Metastatic						
Nodal		1	2	2		
Extra-nodal			1	1	1	1
Nodal and extra-nodal			3			

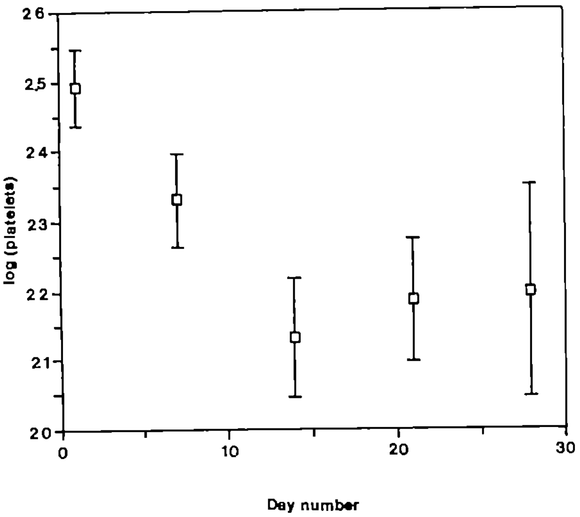

Fig. 4 Platelet count (95% confidence intervals by day)

and of survival has not yet been achieved and exceeds 9 and 12 months respectively in patients achieving a complete response. It is of interest that prolonged survival occurred in patients who achieved disease stabilisation. The initial results of treatment suggest an equivalence to the M-VAC programme, but the duration of follow-up is too short to comment on equivalence in terms of survival. The treatment had considerably fewer side effects than the M-VAC programme. Acute toxicity was acceptable; there was no renal toxicity, no complete alopecia or treatment-related deaths. Haematological toxicity was similar to that of the M-VAC programme. It seems that MVMJ provides an advance on M-VAC combination chemotherapy, producing a similar response rate with considerably fewer side effects. This requires confirmation by extending the study to a larger number of patients.

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Volatile N-nitrosamines in Urinary Catheters

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Summary—Levels of volatile N-nitrosamines were measured in 10 brands of latex and 2 brands of silicone catheters using high performance liquid chromatography. The cytotoxicity of catheters from identical batches was determined by measuring the inhibitory effect of catheter extracts on the uptake of ^{3}H-labelled thymidine into L-929 fibroblasts in culture (IC_{50}).

The most frequently encountered nitrosamines were N-nitrosodi-n-butylamine and N-nitrosodiethylamine. Total N-nitrosamine levels in excess of 100 ng/g were found in 6 of the 16 catheters tested. When compared with the cytotoxicity of the catheters a significant correlation was found, with increasing nitrosamine content being associated with greater cytotoxicity. In view of the reported toxic and carcinogenic effects of these compounds it is suggested that the nitrosamine content of catheters be routinely monitored and safe regulatory limits be imposed.

It is now well established that urinary catheters may cause urethritis and urethral structures. The potential for these adverse effects varies according to the composition of the catheter material, with catheters made of silicone being generally less toxic than those made of latex (Blacklock, 1986). The demand for a screening test to detect and quantify catheter toxicity has led to the development of animal and cell culture methods of toxicity assessment (Nacey *et al.*, 1985, 1986). These methods have confirmed that the toxic effects are due to diffusible toxic compounds within the catheters.

Investigations into the presence of toxic organic compounds contained within rubber baby teats and pacifiers have revealed high levels of volatile N-nitrosamines (Havery and Fazio, 1982). These findings prompted us to investigate the possibility that high levels of volatile N-nitrosamines may be present within urinary catheters, and to determine if there is a significant correlation between any detectable nitrosamine and the degree of catheter toxicity as determined by cell culture testing.

Materials and Methods

Sixteen urinary catheters compromising 10 brands of latex and 2 brands of silicone catheter commercially available in Australasia were used. The catheters were assigned a number from 1 to 16 and both the nitrosamine assay and the toxicity assessment were performed without knowledge of the catheter brand or composition. Non-parametric statistical analyses were performed according to the methods of Brown (1977).

N-nitrosamine assay

Five grams of catheter material, excluding the balloon and valve, were used for each assay. If more than 5 g were available a second assay was performed, so that the entire length of the catheter was analysed. The smaller paediatric catheters provided only 3 g of material suitable for study.

Volatile N-nitrosamines were extracted from the catheter samples using the method of Havery and Fazio (1982). N-nitrosopyrolidine, 200 ng, was added as an internal standard to the methylene chloride extracts after the soxhlet extraction stage. Methylene choride was redistilled from glass before use and was demonstrated to be free of nitrosating

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agents by blank determinations incorporating diethylamine and morpholine. Nitrosamines in the final extracts were detected and quantified by high-performance liquid chromatography (HPLC) with chemiluminescent detection (thermal emission analysis) of N-nitrosamines produced by pyrolysis as described by Weston (1985). Sample injection volumes were 50 µl and the limit of detection was from 1 to 3 ng/g for a 5 g catheter sample. Standard solutions containing N-nitrosodi-n-butylamine, N-nitrosodiethylamine, N-nitrosodimethylamine, N-nitrosopiperidine and N-nitrosopyrolidine, 1, 2, 2, 2 and 5 mg/l respectively were used for quantification, using peak heights. In addition to the hexane-acetone HPLC mobile phase, a second mobile phase, hexane: methylene chloride: acetonitrile, 75: 25: 1.5 by volume, was used to confirm the identification and quantification of the nitrosamines. This mobile phase was able to resolve completely NDEA and NPIP which were not fully resolved by the hexane-acetone mobile phase (Weston, 1985).

The identification of nitrosamines in 7 samples was confirmed by gas chromatography with mass-selective detection. A Shimadzu GC9A gas chromatograph was used with a Shimadzu GP1000 quadrupole mass spectrometer. The column was a BP10 fused silica capillary tube (25 m length, 0.25 µ film thickness) with helium as the carrier gas. The spectrometer was operated in the chemical ionisation mode using isobutane as the reagent gas, and nitrosamine peaks were detected by monitoring the M+1 ions. Retention times were compared with those of similarly chromatographed authentic standards. Although other compounds could give the same M+1 ions as some of the N-nitrosamines, it is unlikely that these would have the same retention time as the nitrosamines and hence would be distinguishable from the N-nitrosamine peak.

Toxicity assessment

Catheters taken from the same batches as those assayed for nitrosamines were analysed for cellular toxicity. Three separate catheters from each batch were analysed, except for catheters 9 and 10 where only one sample of each catheter was available for study. The toxicity assessment was made using the method of Nacey *et al.* (1986). The inhibitory effect of catheter extracts on the uptake of ^{3}H-labelled thymidine by L-929 mouse fibroblasts was measured. Catheter extracts were prepared at concentrations of 6, 9, 13, 20, 30, 44, 67 and 100% (dilution factor = 1.5), with additional extracts at concentrations of 0.001, 0.01 and 0.1%. The concentration of extract which depressed thymidine uptake to 50% of control (IC_{50}) was determined for each catheter.

Results

All of the latex rubber catheters assayed were shown to contain detectable amounts of volatile N-nitrosamines (Table 1). In 6 of these, individual nitrosamine levels were found to be in excess of 100 ng/g. The most frequently detected nitrosamines were N-dinitrosodi-n-butylamine and N-dinitrosodiethylamine. N-nitrosopiperidine was also found in high levels in 2 catheters. N-nitrosodimethylamine was detected in 3 catheters, but in low concentrations. The 2 silicone catheters were found to contain very low or nil levels of nitrosamines.

When compared with the results of the cytotoxicity assays (Table 2), the catheters containing the greatest levels of volatile N-nitrosamines were also shown to be the most toxic to cells in culture. The correlation between total N-nitrosamine levels and the degree of cytotoxicity (IC_{50}) was significant (Spearman's rank correlation coefficient $r_s = -0.846, P < 0.001$).

Discussion

The reported effects on tissue of volatile N-nitrosamines may be divided into two groups: those resulting in acute toxicity and those associated with carcinogenesis. The acute toxic effects of N-nitrosamines have been investigated in several animal studies where sub-lethal doses have been shown to result in hepatic centrilobular toxicity and diffuse pulmonary haemorrhage following parenteral administration (Heath and Magee, 1962). Oral administration has also been found to result in ulceration of the gastric mucosa (Heath and Magee, 1962), while direct instillation into the bladder causes epithelial necrosis (Hicks and Wakefield, 1972). Since the various chemical accelerators, stabilisers and other compounds used during catheter manufacture may themselves be cytotoxic, the toxic effects of available nitrosamine *per se* on the urethral mucosa are not known. However, the results of this investigation have demonstrated a significant correlation between the levels of volatile N-nitrosamines in catheter extracts and the degree of cytotoxicity, which suggests that these compounds may contribute to the urinary catheter toxicity observed both clinically and experimentally.

Table 1 Volatile N-Nitrosamine Levels in Urinary Catheters as Determined by HPLC

			N-Nitrosamine Levels (ng/g)				
Catheter number	*Number of replicates*	*Type*	*NDBA*	*NDEA*	*NPIP*	*NDMA*	*Uncharacterised responses**
1	2	Latex	20+t, 30	90+t, 90	20, 50+t	tr, 2.5	30, 100
2	2	Latex	100, 110t	ND	ND	ND	
3	2	Latex	150, 180+t	ND	ND	ND	
4	2	Latex	100t, 250	ND	ND	ND	
5	2	Latex	ND	60+t, 160	ND	tr, 5	
6	2	Latex	3.5t, 17	ND, 7	ND	ND, 8	
7	1	Latex	17	ND	ND	ND	
8	1	Silicone	ND	4 5+	10+	ND	
9	2	Latex	ND	360+t, 2500	ND	ND	370+, 3400
10	1	Silicone	ND	ND	ND	ND	
11	1	Latex	13	ND	ND	ND	
12	1	Latex	ND	ND	140+S	40+	
13	1	Latex	ND	30	ND	ND	
14	1	Latex	15	19	ND	ND	
15	1	Latex	ND	20	ND	ND	
16	1	Latex	ND	30	ND	ND	

NDBA = N-nitrosodi-n-butylamine, NDEA = N-nitrosodiethylamine; NPIP = N-nitrosopiperidine; NDMA = N-nitrosodimethylamine.

ND = None detected.

tr = Trace amounts detected.

*Calculated assuming a molar response equivalent to N-nitrosopyrrolidine, not confirmed as an N-nitrosamine.

+ Identity and quantification checked by use of the second HPLC solvent system

t Identity confirmed by semi-quantitative gas-liquid chromatographic mass-spectral data

S Identity confirmed by qualitative gas-liquid chromatographic mass-spectral data.

Table 2 Total Volatile N-Nitrosamine Concentrations Compared with L-929 Fibroblast IC_{50} Toxicity Levels

Catheter number	*Number of replicates*	*Total N-nitrosamine levels (ng/g)*	*L-929 fibroblast IC_{50}*
1	2	160, 272.5	22.3
2	2	100, 110	
3	2	150, 180	8.1
4	2	100, 250	
5	2	60, 165	43 0
6	2	3 5, 32	86.0
7	1	17	
8	1	14 5	71 7
9	2	730, 5900	0.01
10	1	None detected	Non-toxic
11	1	13	52.0
12	1	180	19 7
13	1	30	46 0
14	1	34	
15	1	20	41.0
16	1	30	52 0

The carcinogenic properties of nitrosamines are well established (Craddock, 1983). Experimental animal models have shown parenterally administered nitrosamine to be associated with primary hepatic and renal carcinoma. Nitrosamines administered locally and by intravenous and subcutaneous routes have been found to cause carcinoma of the oesophagus, stomach and bladder. In all cases these were observed to be squamous cell carcinomas on histological examination (Okada *et al.*, 1975). Recent clinical trials have reported an increased incidence of squamous cell carcinoma of the bladder in patients with long-term indwelling urinary catheters (Kaufman *et al.*, 1977; Locke *et al.*, 1985). The similarity in morphology of nitrosamine-induced experimental carcinomas to those found following long-term urinary tract catheterisation raises the possibility that nitrosamines may be a causative agent in the development of catheter-associated malignancy. While the chronic effects of low doses of nitrosamines on transitional epithelium are poorly understood and the development of malignancy is unproven, there can be little doubt as to the potential for immediate cellular toxicity as demonstrated in this study.

The origin of nitrosamines within the rubber products has been the subject of some speculation. Previous reports have shown that both amines and a nitrosating agent must be present for a nitrosamine compound to form (Havery and Fazio, 1982). The source of the amines is most probably the chemical accelerators and stabilisers used during the vulcanisation process, *e.g.* dialkyl dithiocarbamates and dialkylthiuram mono and polysulphides. The specific nitrosating agents are not known, but are likely to be retardants or associated compounds used during vulcanisation and several compounds related to nitrosodiphenylamine have been suggested (McGlothin *et al.*, 1981). The toxic and possible carcinogenic effects of nitrosamines in rubber products indicate that attempts should be made to reduce the nitrosamine content of urinary catheters. The most obvious and perhaps most effective way of achieving this is to reformulate the catheter composition and use silicone or some of the wide range of alternative accelerators which are non-nitrosatable (Spiegelhalder and Preussman, 1982; Preussmann, 1984). In rubber formulations where amines or amine derivatives are essential, the use of so-called "safe amines" which give rise to non-carcinogenic nitrosamine derivatives should be considered (Eisenbrand *et al.*, 1980).

The potential for adverse effects has been recognised in West Germany, USA, Canada and Scandinavia, where the health authorities have set an upper limit of 10 ng/g of total nitrosamines in teats and pacifiers (Food and Drug Administration, 1984). To date no such limits have been produced for urinary catheters despite numerous reports of catheter-induced urethral strictures and the association between long-term catheter drainage and carcinoma. In view of this we suggest that nitrosamine determinations be added to the various catheter standardisation tests that are undertaken, and that those catheters exhibiting high levels of nitrosamines should be avoided in clinical practice.

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Oestrogen in the Treatment of Prostatic Carcinoma

What is the Safe and Effective Dose of Ethinyloestradiol?

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Summary—The treatment of prostatic carcinoma with diethylstilboestrol (DES) and ethinyloestradiol (Lynoral) has become less popular since the introduction of new forms of treatment such as antiandrogens, estramustine phosphate and LHRH analogues. One of the reasons for this decline in popularity is the risk of cardiovascular side effects during treatment with oestrogens.

In the literature, different dosages of DES and ethinyloestradiol are recommended and different rates of cardiovascular side effects are reported. In a prospective study, 18 patients were treated with ethinyloestradiol 0.05 mg/day. In most cases this lowered the plasma testosterone permanently below castrate level during therapy. Also, because the acid phosphatase returned to normal in almost all patients, this treatment seemed adequate. In 4 patients the treatment was stopped because of side effects, in 3 of these because of cardiovascular complications. The cardiovascular side effect at this dose are considerable (29%) but comparable rates are reported in some studies following placebo treatment of patients with prostatic carcinoma.

With the development of new forms of treatment of prostatic cancer, *e.g.* LHRH analogues, it is interesting to consider the traditional oral oestrogen therapy. Since Huggins and Hodges (1941) and Herbst (1941) reported that testosterone promoted the growth of prostatic carcinoma and that castration or treatment with oestrogens could inhibit this growth, many patients have been treated in this way, either by oestrogens or by bilateral orchiectomy. Nowadays many urologists prefer orchiectomy because of its simplicity and efficacy. This has been the case in this hospital, but oestrogen treatment has also been used frequently in the past. However, oestrogen therapy seems to have been responsible for an increase in cardiovascular and thrombo-embolic complications (Blackard *et al.*, 1970; Byar, 1973; Blackard, 1975; Abbou, 1980). Several reasons have been given for this phenomenon, namely a decrease in serum albumin, in serum antithrombin factor III, in serum fibrinolytic activity, and an increase in plasma volume (Dobbs, 1980; Vahrenhorst, 1982). The studies by the Veterans Administration Cooperative Urological Research Group (VACURG) were particularly important. According to their first report (VACURG, 1967a), oestrogen treatment had almost the same survival rate as treatment with placebo. In this first study, mortality appeared to be due mainly to cardiovascular complications from the oestrogen treatment and not from the prostatic carcinoma itself. Because of this it was advised that the dose of DES be reduced from 5 to 1 mg/day. In later studies (VACURG, 1967b) this dosage appeared to be effective and fewer cardiovascular side effects were noted (Bailar *et al.*, 1970; Byar, 1973; Pollen, 1983). However, with a dosage of 1 mg/day, Shearer, *et al.* (1973) and Prout *et al.* (1976) found in only 50% of patients a plasma testosterone below castrate level (<2 nmol/l) and 3 mg/day were recommended.

The lowering of plasma testosterone below castrate level is regarded as a simple parameter for effective treatment (Shearer *et al.*, 1973; Beck *et al.*, 1978; Flora Esteva *et al.*, 1980; Bishop *et al.*,

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1985). Robinson and Thomas (1971), Flores Esteva *et al.* (1980) and Altwein and Jacobi (1980) confirmed a lowering of plasma testosterone below castrate level with a dosage of 3 mg DES per day. A higher dose did not reduce the level any further.

In the Netherlands and elsewhere the use of DES has been discontinued, largely because of the negative publicity given to its use in habitual abortion (vaginal carcinoma in so-called DES-daughters) and the synthetic oestrogen ethinyloestradiol is used instead. As with DES, different dosages are reported: 1 mg/day (Smith, 1981), 0.2 mg/day (Altwein and Jacobi, 1980); 0.5 mg *tid* (Shearer *et al.*, 1973) and 0.05 mg once a day (de Voogt *et al.*, 1980).

In recent years, new palliative treatments have been described: cyproterone acetate (Smith *et al.*, 1973), estramustine phosphate (Kjaer *et al.*, 1975), prolactin inhibitors (Jacobi, 1979) and LHRH analogues (Tolis, 1981, 1982; Waxman *et al.*, 1983; Faure, 1984). None of these has proved more effective than either oestrogen or bilateral orchiectomy. Their advantages lie in fewer side effects. In order to decide whether or not ethinyloestradiol is a good and inexpensive palliative treatment of prostatic carcinoma, the lowest effective dosage has yet to be established. It has also to be decided whether or not this dose is safe, *i.e.* that the side effects (particularly cardiovascular) are acceptable. The aim of this study was to confirm that in our patients the lowest known dose of ethinyloestradiol (0.05 mg/day) could reduce plasma testosterone to less than the castrate level. The side effects were also noted.

Patients and Methods

Between January 1983 and July 1986, 18 patients were treated for prostatic carcinoma with ethinyloestradiol 0.05 mg/day. Their mean age was 74.3 years (range 58–88). In all cases the diagnosis was confirmed histologically by needle biopsy or transurethral resection. All patients were staged by digital rectal examination, prostatic acid phosphatase measurement, bone scan and bone survey. Treatment was started because of obstructive voiding difficulties or bone pain caused by bone metastases. Staging and grading are summarised in Table 1. One patient was excluded from the study because of inappropriate intake of medicine. Patients with underlying atherosclerotic disease or a history of thrombo-embolism were excluded. Each patient was evaluated at varying intervals for side effects. To determine the efficacy of the treatment, plasma testosterone and prostatic acid phosphatase were measured during follow-up.

Table 1 Staging (according to TNM classification) and Grading of Prostatic Cancer in 17 Patients Treated with Ethinyloestradiol 0.05 mg/day

Stage	*No of patients*	*Grade*	*No. of patients*
T2 NX MO*	1	GI	3
T3 NX MO*	2	GII	9
T4 NX MO	7	GIII	5
T4 NX M1	7		

* Patients not selected for curative treatment because of poor general condition and/or age

Results

After 1 month's treatment with ethinyloestradiol 0.05 mg/day the mean plasma testosterone was reduced from 19.1 ± 7.8 nmol/l (before treatment) to 2.2 ± 0.9 nmol/l; 33% of the patients already had a testosterone level below castrate level (< 2.0 nmol/l). After treatment for 2 more months the mean testosterone level was even lower (1.6 ± 0.7 nmol/l). At this time 76% of the patients had a plasma testosterone below castrate level; 3 patients were near this level (2.1, 2.4 and 2.7 nmol/l) (Table 2). One year after treatment the mean plasma testosterone was still below castrate level (1.7 ± 0.75 nmol/l).

With regard to serum prostatic acid phosphatase, it was noted that after 1 month's treatment nearly all values had returned to normal (< 1 u/l; 0.52 ± 0.21 u/l). In all patients this effect appeared to be permanent during follow-up. Serum prostatic acid phosphatase was 0.79 ± 0.39 u/l after 3 months (Table 2) and 0.66 ± 0.32 u/l after 1 year. The mean follow-up was 15.6 months (range 3–28).

Several side effects were noted during treatment (Table 3), which had to be stopped in 4 cases: painful gynaecomastia (1), cardiac failure (1) and deep venous thrombosis (2). Five patients had cardiovascular side effects (29%). None died during follow-up.

Discussion

The level of plasma testosterone is usually regarded as a simple and reliable indication of the effectiveness of hormone treatment for prostatic carcinoma (Shearer *et al.*, 1973; Beck *et al.*, 1978; Flores Esteva *et al.*, 1980; Bishop *et al.*, 1985). Ethinyloestradiol 0 05 mg, taken once a day, proved sufficient to lower plasma testosterone permanently below

Table 2 Plasma Testosterone and Prostatic Acid Phosphatase before and during Treatment with Ethinyloestradiol 0.05 mg/day

	Testosterone (nmol/l)		*Prostatic acid phosphatase (u/l)*	
No of patients	*Before treatment*	*After 3 months' treatment*	*Before treatment*	*After 3 months' treatment*
1	37.4	0.6	0.18	0.20
2	15.8	2.4	8.98	0.52
3	25.9	—	1.09	0.84
4	—	1.6	3.54	0.34
5	16.2	1.8	0.98	—
6	17.4	2.0	1.24	1.28
7	19.1	1.4	0.74	0.62
8	13.3	0.8	3.68	0.93
9	21.2	0.2	3.71	0.26
10	14.0	1.9	2.81	0.21
11	20.3	1.8	7.41	0.63
12	16.2	1.7	0.66	0.38
13	—	2.7	1.22	—
14	—	1.7	—	0.61
15	7.5	0.5	3.58	0.47
16	12.3	1.7	24.07	3.90
17	32.1	2.1	0.88	—
Mean value (±S.D.)	19.1 (±7.8)	1.6 (±0.7)	4.05 (±2.61)	0.79 (±0.39)

castrate level. Some investigators found a slight increase in circulating plasma testosterone about 6 months after orchiectomy (Robinson and Thomas, 1971). This was also seen after chemical castration (Altwein and Bandhauer, 1976; Beck *et al.*, 1978). No explanation could be given for this. In our patients no increase in plasma testosterone was seen during treatment.

Several different percentages have been given in the literature concerning cardiovascular side effects during hormone treatment. One explanation is the varying dosages of ethinyloestradiol which were used. In addition, Blackard *et al.* (1970) noted during placebo treatment of prostatic carcinoma a morbidity and mortality rate of 24% as a result of cardiovascular side effects. Bailar *et al.* (1970) found a mortality rate of 37.5% from cardiovascular side effects during placebo treatment of patients with Stages III and IV prostatic carcinoma. A similar percentage was found in the first VACURG study (VACURG, 1967a). Hendrikssen and Edhag (1986) noted a higher incidence of cardiovascular side effects in patients receiving oestrogens compared with those undergoing orchiectomy, despite using a very low dose of oestrogen.

Table 3 Side Effects of Treatment with Ethinyloestradiol 0.05 mg/day

Side effects	*No. of patients*	*%*
Painful gynaecomastia	3	18
Nausea/anorexia	2	12
Hypertension (diastole > 100 mmHg)	1	6
Ankle oedema	6	35
Cardiovascular side effects	5	29
deep venous thrombosis (2)		
congestive heart failure (1)		
myocardial infarction (2)		

Marx (1975) stated that the presence of prostatic carcinoma itself led to a diffuse intravascular coagulation syndrome in 20% of their patients. It is true that we had a high morbidity rate (29%) from cardiovascular side effects, but similar rates have been noted during placebo treatment of comparable groups of patients. Whether or not new forms of treatment, such as LHRH analogues, will result in significantly less cardiovascular morbidity, remains to be seen.

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Urethral Substitution in Women

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Summary—A series of 30 female patients underwent total urethral substitution for a variety of conditions, usually urogenital sinus abnormalities or post-irradiation vesicourethrovaginal fistulae. Five different techniques were used: bladder flap neourethroplasty, neourethroplasty using a urinary tract remnant, vaginal/urogenital sinus neourethroplasty, pedicled labial skin tube neourethroplasty and colonic substitution neourethroplasty with synchronous implantation of an artificial sphincter.

Bladder flap neourethroplasty is appropriate if the bladder size is adequate and if the bladder neck is incompetent, but stress incontinence is a common complication which must be anticipated and dealt with proleptically. Vaginal/UG sinus neourethroplasty is preferred if the bladder neck is competent enough to preserve continence. When no other tissue is available, particularly after radiotherapy, a pedicled labial skin tube neourethroplasty gives the best results. Colonic substitution with the implantation of an artificial sphincter is not satisfactory.

Any surgically created neourethra should be wrapped with either labial fat pads or omentum and, in the absence of a competent bladder neck, with an artificial sphincter cuff to support the urethra and to prevent it telescoping, and for use as a back-up if continence is not adequate.

Total urethral substitution is not often required in females and most reports on the subject have been on single cases or small series (Gunst *et al.*, 1987). Because of insufficient numbers it is not possible to decide on the basis of these reports which of the available procedures would be most useful for any given circumstance.

Experience with total urethral reconstruction in 30 females has allowed such decisions to be made and this report describes this experience.

Patients and Methods

Thirty patients aged between 8 and 62 years have undergone total urethral reconstruction. The underlying causes and procedures used are shown in Tables 1 and 2. The commonest causes were urogenital sinus/cloacal malformations, post-hysterectomy/post-irradiation vesicourethrovaginal fistulae, and exstrophy, but the series also included 2 girls with severe iatrogenic trauma, 2 with severe damage to the lower urinary tract following road traffic accidents and 1 who had had a cystourethrectomy for malignancy.

The bladder flap neourethroplasty (NUP) involved raising an obliquely orientated flap of anterior bladder wall with the base of the flap aimed towards the vascular pedicle on one side. The length to breadth ratio was between 4 and 6 to 1. The inferior margin of the flap was orientated to form the posterior margin of a suitably sited bladder neck and the remainder of the flap was formed into a tube by closing the mucosa snuggly around a 16F Foley catheter and then replacing it with a 12F catheter and closing the muscle layer, which had

Table 1 Indications for Urethral Reconstruction

Urogenital sinus/cloaca	11
Post-irradiation/hysterectomy	9
Failed exstrophy closure	5
Iatrogenic	2
Road traffic accident	2
Cystourethrectomy	1
Total	30

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Table 2 Procedures

	Bladder flap	*Bladder remnant*	*Vaginal*	*Labial*	*Colon +AUS*
UG sinus/cloaca	4	—	7	—	—
Post-irradiation	—	—	—	7	2
Exstrophy failures	—	3	—	—	2
Others	2	1	1	1	—
Total	6	4	8	8	4

the effect of narrowing the neourethra down to about that calibre. The "catheterisability" of the neourethra was ensured at this stage before completing the procedure. The NUP was then wrapped with omentum and an artificial sphincter cuff wrapped around that with more omentum around the cuff if possible. The plugged off sphincter cuff tubing was then brought out into the groin, where it was accessible for implantation of the remainder of the device if this subsequently proved to be necessary. The 12F catheter was left in for about 10 days.

The urinary tract remnant NUP was used in 3 children with exstrophy and 1 who had lost almost the entire lower urinary tract in a road traffic accident. The same principles were employed in constructing a neourethral tube from the remnant as with bladder flap NUP. In each case the neourethra was anastomosed to a pouch-type substitution cystoplasty.

The vaginal/UG sinus NUP technique was used principally in patients with urogenital sinus and cloacal abnormalities. We regard urogenital sinus abnormalities as being of 4 types with either a high or a low confluence and the urogenital sinus having the configuration of either a urethra into which the vagina enters, or a vagina into which the urethra enters. The vaginal flap NUP was used in patients who had a urogenital sinus with a high confluence and the configuration of a vagina into which the urethra entered, particularly if the bladder neck was competent. The latter is now regarded as the main criterion for using this technique, whatever the aetiology of the problem. The principles used in forming the neourethra were the same as for the bladder flap technique.

Some of these girls have an acontractile bladder urodynamically as well as a competent bladder neck and will therefore be dependent on clean intermittent self-catheterisation (CISC) to void. There are advantages in such circumstances in advancing the neourethra, and thus the meatus, to the underside of the clitoris: firstly, the meatus is easier to find for catheterisation; secondly, the extra length may enhance continence (Hendren, 1980); thirdly, and most importantly, it is easier to get into the right plane for extension up the anterior vaginal wall and around the bladder neck without damaging the latter by opening up the plane distally at first. Meatal advancement was therefore used routinely.

The disadvantage of the vaginal/sinus NUP is that it leaves rather a large defect in the anterior vaginal wall that usually requires closure with a skin flap, although primary closure is occasionally possible. The buttock flap described by Hendren (1980) was the skin flap most commonly used, although it has the disadvantage of requiring a second procedure at a later date to divide the pedicle of the flap and restore the vulval anatomy to normal.

The labial skin tube technique was developed specifically to deal with complex vesicovaginal fistulae following radiotherapy and a hysterectomy in which the urethra is effectively if not actually destroyed (Mundy, 1988). Like urinary tract remnant NUP, it is usually used in combination with substitution cystoplasty, although the neourethra can be anastomosed directly to the bladder or to a competent bladder neck. The advantage of the labial skin tube technique is that an "anti-reflux" anastomosis to the substitution cystoplasty is possible to provide a continence mechanism without the need for an artificial sphincter. The same technical principles are used as with bladder flap and other types of NUP. Like the extended vaginal/sinus NUP, the meatus ends up just below the clitoris for ease of catheterisation.

Four patients underwent colonic substitution of the urethra with wrapping of an artificial sphincter cuff around the distal end of what was effectively a colonic substitution cystourethroplasty. To maintain the vascularity of the colon distal to the artificial sphincter cuff the cuff was placed carefully within a vascular arcade, not around it.

Results (Table 3)

Two of the four patients who underwent colonic substitution with an artificial sphincter, both with post-irradiation fistulae, had persistent incontinence and subsequently required an ileal conduit urinary diversion. Of the 4 girls who underwent remnant NUP, 1 had to have the artificial sphincter cuff removed because of infection. Another device was implanted uneventfully 14 months later. One of the girls who had a vaginal NUP developed a mild "urethral" stricture, presumed to be related to scarring from previous surgery, but this is controlled by the intermittent self-catheterisation that she now uses for voiding. Of the labial skin tube NUP patients, 1 subsequently died of metastatic disease (carcinoma of the cervix) and 1 of the remainder was incontinent, presumably because the submucosal tunnel by which the neourethra was anastomosed to the substitution cystoplasty became ischaemic and broke down. The incontinence has since been controlled by devising a particular type of artificial sphincter to produce the same sort of compression effect as a Kaufmann prosthesis.

The remaining patients all had a satisfactory result, although 50% of those who had an artificial urethral sphincter (AUS) cuff implanted during their primary procedure (*i.e.* bladder flap or remnant NUP) required implantation of the remainder of their artificial sphincter to achieve total continence. Continence was adequate in the remainder but not usually perfect: 5 of the 9 patients with a labial NUP, half with a vaginal NUP and 1 with a bladder flap NUP use CISC to void. The remainder void spontaneously.

Discussion

The problem with these patients is not so much where to find tissue with which to make a urethra, but how to secure continence and at the same time adequate bladder emptying. The latter is less of a problem because if the patient is unable to void voluntarily, then CISC can be used. The most important factor in this respect is to ensure an easily catheterisable neourethra and one must be sure that the neourethra is easily catheterisable before completing the operation. It seems to be common practice to construct a neourethra around a catheter and then simply to leave it as it is until the catheter is removed 2 or 3 weeks post-operatively. Under these circumstances, irregularities or false passages that prevent adequate self-catheterisation cannot be discovered until it is too late.

Table 3 Complications

Bladder flap NUP	SWI* in 4 (50%) → Remainder of AUS
Remnant NUP	SWI in 2 (50%) → Remainder of AUS AUS infection in 1 (25%) → Revision
Vaginal/sinus NUP	Neourethral stricture in 1 (12 5%) → CISC
Labial NUP	1 died with metastases (12 5%) 1 wet—anastomotic breakdown (12 5%)
Colon + AUS	SWI in 2 (50%) → Diversion

*SWI. sphincter weakness incontinence.

Continence is more of a problem. If the bladder neck is intact and functioning, it is obviously of paramount importance not to do anything that might compromise its function and for these reasons a vaginal urethroplasty is the most appropriate procedure; if previous surgery, trauma or radiotherapy prohibit it, the pedicled labial skin tube NUP is appropriate. The most common situation where this technique is indicated is in a patient with a urogenital sinus type of abnormality who has a high confluence and the configuration of a very short urethra (maybe no more than just a bladder neck) emptying into a vagina-like UG sinus. The disadvantage of this technique is the need to replace the anterior vaginal wall that has been used for the NUP with a skin flap, usually a buttock flap, although this is not always necessary. Even if closure is possible without a flap, it is often inadvisable because late vaginal stenosis is difficult to deal with satisfactorily.

If the bladder neck is not competent, then continence is bound to be precarious whatever is done. If the patient has a bladder of normal size, a bladder flap NUP is possible without the need for augmentation or substitution cystoplasty to make up the deficit of bladder thereby incurred. It is easier to make a bladder than a urethra and if there is only a small bladder remnant, this remnant should be formed into a tube for the neourethra with a substitution cystoplasty on top, preferably a pouch type to ensure the lowest possible intravesical pressure. In both instances the absence of a competent bladder neck means that stress incontinence is a common complication. Because achieving continence with the NUP alone is unpredictable, the combined omentum and AUS cuff wrap is recommended. The author's impression is that the wrap in itself is valuable but the main advantage is that if there is post-operative incontinence, the remainder of the AUS can be implanted without the need to reopen the pelvis and run the risk of damaging the neourethra.

If none of these approaches is possible, which usually means that the patient has had a cystourethrectomy, or if the tissues have been so irradiated or traumatised that any bladder or urethral remnant is useless, there are theoretically two options. The first is to use a gut substitution technique. One such technique, as described above, is a colonic cystourethroplasty (or any other type of cystourethroplasty, depending on the surgeon's inclination) with an artificial sphincter around the lower end of it to provide continence. Unfortunately, this does not work often enough to make it a valuable technique.

The artificial sphincter was designed to compress a conduit with a configuration of the urethra and attempting to compress anything with the configuration of small or large bowel seems doomed to failure. Not only are the overall circumference and lumen too large but the wall of the viscus is too thin, so that even if the gut is tailored to reduce its calibre, the result is akin to trying to squeeze a sock between three cushions. On the two occasions we have made the system work, it was by tethering the gut wall outwards so that the anterior and posterior walls were in apposition and then using a large sphincter cuff, also tethered out so that it produced anteroposterior compression with two cushions rather than the three cushion shape it tends to adopt under normal circumstances. The technique is not recommended.

The author has on two occasions (neither of which is included in this series) used a technique of ileal substitution NUP with intussusception into a substitution cystoplasty to provide a continence mechanism. The patients voided by CISC. This is not a satisfactory technique because it is often not possible to get ileum down to the external meatus, because catheterisation is often difficult and because of the irritating mucus discharge from the neourethra. This is therefore another technique that the author feels should only be used as a last resort.

The alternative to gut substitution (and, in the author's experience, a much better approach) is the pedicled labial skin tube NUP, this has the advantage not only of providing a well vascularised tube graft, but also one that can be anastomosed to a substitution cystoplasty with a tunnel-type technique to produce a continence mechanism similar to the anti-reflux system obtained by the Leadbetter-Politano ureteroneocystostomy. The patient then voids by CISC, although nearly half of our patients were eventually able to void spontaneously and yet remain continent between times.

It is concluded that when the bladder neck is competent a vaginal neourethroplasty should be performed unless the vaginal wall is too scarred, in which case a labial skin tube is used. If the bladder neck is incompetent but the bladder is of good size, a bladder flap NUP is performed. If the bladder remnant is small, as in an exstrophy failure for example, this remnant is best turned into a urethra with a substitution cystoplasty above, although if sufficient bladder remains an augmentation cystoplasty may suffice. If the patient has had a cystourethrectomy, if the tissues are heavily irradiated or if a cystourethroplasty is required, a pedicled labial skin tube urethroplasty is the best option.

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The Effect of Spermine, Spermidine and Kallikrein on the Triple Adenosine Triphosphatase Enzyme Activity of Spermatozoa in Males with Oligoasthenozoospermia

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Summary—Unknown factors in the seminal plasma of normal semen that affect the motility of spermatozoa have a positive effect on adenosine triphosphatase (ATPase) enzyme activity. In an attempt to produce such an effect, spermine, spermidine and kallikrein were added to the incubation media in which spermatozoal ATPase enzyme activity was determined. These seminal substances increased the triple ATPase enzyme activity of spermatozoa from oligoasthenozoospermic men. We propose that the ATPase enzyme activity of spermatozoa may indicate sperm motility as a biochemical test.

The ATPase enzyme activity of spermatozoa from oligoasthenozoospermic men is lower than that of normal subjects (Ronquist *et al.*, 1977; Stegmayr *et al.*, 1980; Karacagil *et al.*, 1984, 1985). Spermine, spermidine (Goueli *et al.*, 1985) and kallikrein (Schill *et al.*, 1979; Fink *et al.*, 1985) increase sperm motility. The aim of this study was to determine the effect of these seminal substances on the triple ATPase enzyme activity of washed spermatozoa from oligoasthenozoospermic men and to assess the possibility of a biochemical test of sperm motility.

Patients and Methods

Spermiograms were carried out according to the method described by Amelar *et al.* (1973) on 42 oligoasthenozoospermic men and 19 healthy volunteers. The procedures for the centrifugation of semen samples, the washing of pellet I and the determination of triple ATPase enzyme activity were in accordance with our previous work (Karacagil *et al.*, 1984, 1985).

Results

In a preliminary study of 10 normal subjects and 10 oligoasthenozoospermic men the maximum level of ATPase enzyme activity for spermine, spermidine and kallikrein was obtained with 5 mM, 0.5 mM and 5 u concentrations respectively. These concentrations were used throughout the study. The results are shown briefly in Tables 1 to 4.

Discussion

By definition, oligoasthenozoospermic men have a statistically lower percentage of motile spermatozoa than normal men (Hotchkiss, 1970) (Table 1). Triple ATPase enzyme activity in washed spermatozoa from oligoasthenozoospermic men was significantly lower than that of normal subjects (Table 2). However, the link between sperm motility and ATPase activity remains unproven from these data.

We found that the triple ATPase enzyme activity reached a maximum level when 5 mM spermine and 0.5 mM spermidine were added to the standard incubation medium which was used to determine ATPase activity. These doses were in accord with the amounts of spermine and spermidine in seminal plasma from normal men (Coffey, 1986).

It was reported that prostatic spermine and spermidine stimulated the phosphorylation reaction (Goueli *et al.*, 1985). The triple ATPase enzyme activity of washed spermatozoa from oligoasthenozoospermic men was stimulated by the addition of

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Table 1 Characteristics of Semen from Normal and Oligoasthenozoospermic Men

Groups	*Sperm density (million/ml) ± SE*	*Normal morphological feature (%) ± SE*	*Motility (%) ± SE*
Normal (n = 19)	69.5 ± 5.1	88.9 ± 1.2	74.7 ± 2.9
Oligoasthenozoospermic (n = 42)	19.8 ± 2.2	62.7 ± 1.8	17.9 ± 1.8
P	<0.01	>0.01	<0.01

Table 2 Mean Values of Triple ATPase Enzyme Activity (nmol P_i/mg protein/h) of Washed Spermatozoa from Normal and Oligoasthenozoospermic Men

Groups	*Na^+/K^+–Mg^{2+} ATPase ± SE*	*Mg^{2+}ATPase ± SE*	*Ca^{2+}–Mg^{2+} ATPase ± SE*
Normal (n = 19)	1407.8 ± 79.7	2413.9 ± 35.7	4430.5 ± 45.6
Oligoasthenozoospermic (n = 42)	1134.3 ± 30.6	2193.7 ± 22.7	3825.5 ± 48.9
P	<0.01	<0.01	<0.01

Table 3 Effects of Spermine, Spermidine and Kallikrein on Triple ATPase Enzyme Activities (nmol P_i/mg protein/h) of Normal Spermatozoa

Groups	*Na^+/K^+–Mg^{2+} ATPase ± SE*	*Mg^{2+}ATPase ± SE*	*Ca^{2+}–Mg^{2+} ATPase ± SE*
NS (n = 19)	1407.8 ± 79.7	2413.9 ± 35.7	4430.5 ± 45.6
NS + spermine (n = 19)	1483.0 ± 47.9	2417.2 ± 42.3	4384.6 ± 43.3
P	>0.05	>0.05	>0.05
NS + spermidine (n = 19)	1451.3 ± 46.9	2461.3 ± 42.3	4381.7 ± 60.0
P	>0.05	>0.05	>0.05
NS + kallikrein (n = 19)	1581.4 ± 45.1	2610.5 ± 56.7	4653.1 ± 69.6
P	<0.05	<0.01	<0.01

NS = Normal spermatozoa

Table 4 Effects of Spermine, Spermidine and Kallikrein on Triple ATPase Enzyme Activity (nmol P_i/mg protein/h) of Oligoasthenozooic Spermatozoa

Groups	*Na^+/K^+–Mg^{2+} ATPase ± SE*	*Mg^{2+}ATPase ± SE*	*Ca^{2+}–Mg^{2+} ATPase ± SE*
OS (n = 42)	1134.3 ± 30.6	2193.7 ± 22.7	3825.5 ± 48.9
OS + spermine (n = 42)	1311.9 ± 38.7	2339.9 ± 29.4	4095.3 ± 67.8
P	<0.01	<0.01	<0.01
OS + spermidine (n = 42)	1284.0 ± 36.7	2328.5 ± 26.3	4162.1 ± 65.3
P	<0.01	<0.01	<0.01
OS + kallikrein (n = 42)	1485.2 ± 41.6	2512.9 ± 29.0	4593.8 ± 51.3
P	<0.01	<0.01	<0.01

OS = Oligoasthenozooic spermatozoa.

spermine (Table 4). Spermidine was less effective. This result is similar to that observed by Goueli *et al.* (1985). On the other hand, spermine and spermidine did not stimulate the triple ATPase activity in normal men (Table 3). This may be related to the concentrations of spermine and spermidine in the seminal plasma of normal and oligoasthenozoospermic men. Further work is needed on the kinetics of these enzymes.

The triple ATPase enzyme activity of washed spermatozoa reached a maximum level in the presence of 5 u kallikrein, a dosage similar to that reported by Schill *et al.* (1979) which increased the motility of weakly motile spermatozoa *in vitro*. Kallikrein affected the triple ATPase enzyme activity of washed spermatozoa both in normal and in oligoasthenozoospermic men (Tables 3 and 4). Kallikrein identified in the prostatic tissue and secretions might be involved in the regulation of sperm motility (Fink *et al.*, 1985). It may be hypothesised that this effect is the biochemical result of ATPase activity.

There is a factor or factors in normal seminal plasma that increases the motility of poorly motile sperm (Rozin, 1958; Mitchell *et al.*, 1976). These factors might be zinc (Karacagil *et al.*, 1985), spermine, spermidine or kallikrein and the spermatozoal ATPase enzyme activity might reflect sperm motility biochemically.

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Epididymo-orchitis and Brucellosis

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Summary—A series of 40 patients presented with epididymo-orchitis between January 1983 and August 1985. In 14 brucellosis was diagnosed. In 10 of these (72%) both testis and epididymis were involved and 1 had bilateral disease. All patients with brucella epididymo-orchitis were treated with streptomycin and tetracycline and complete resolution occurred in 8 (57%).

Brucellosis is a cause of human disease, especially in regions whose brucellosis in animals is enzootic.

Distinguished from other fevers in 1861 by Marston, a specific pathogen was first recognised in 1887 by Bruce and its clinical features were comprehensively described in 1897 by Hughes. The complications of brucellosis can be due to the involvement of many systems and in this report we describe our experience in the diagnosis and treatment of brucella epididymo-orchitis.

Patients and Methods

A diagnosis of epididymo-orchitis was made in 40 patients admitted between January 1983 and August 1985. All were febrile, complaining of acute scrotal pain and swelling with, on examination, tender enlargement of the testis and/or epididymis.

Laboratory tests included a complete blood count, erythrocyte sedimentation rate, liver function tests and urine analysis with bacterial culture and antibiotic sensitivity tests of midstream urine. Three blood cultures were performed on every patient within the first 3 days of admission. The tests used to demonstrate brucella antibodies were the Rose-bengal plate test and the standard agglutination test. A titre of 1 : 160 or more in the standard agglutination test was interpreted as evidence of infection (Christie, 1980). Intravenous urography was performed in 35 patients.

All were treated initially with ampicillin or co-trimoxazole in standard dosage. Those in whom brucella antibody tests were negative either remained on the same regime or were given different treatment because of a poor clinical response or as a result of sensitivity tests. When the diagnosis of brucella epididymo-orchitis was confirmed a regime of oral tetracycline 2 g/day for 6 weeks and intramuscular streptomycin 1 g/day for 2 weeks was substituted.

Results

Non-brucella epididymo-orchitis

This group comprised 26 patients aged 14 to 65 years (mean 37). They presented with painful testicular swelling, fever of varying degree and minimal general symptoms. Sixteen (62%) had symptoms of urinary tract infection. In 22 (82%) the leucocyte count exceeded 10,000 mm^3 and in a few cases it reached 30,000 mm^3. Urine culture was positive in 8 patients (*Escherichia coli* in 5, *Proteus* in 2 and *Pseudomonas* in 1). Intravenous urography showed an enlarged prostate in 2 patients and renal stones in 1. Renal and liver function tests were normal.

Ampicillin was effective in 15 patients (58%), although in 3 (12%) gentamicin was added; 11 (42%) responded to co-trimoxazole, urotrate being added in 3 (12%).

Resolution of swelling and complete relief of pain occurred in 21 patients (81%) but 5 (19%) developed complications necessitating orchiectomy (Table). Two patients had tuberculosis epididymo-orchitis.

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Table Results of Treatment

	No. of patients	*Recovery*	*Residual disease*	*Orchiectomy*
Non-brucella epididymo-orchitis	26	21	0	5
Brucella epididymo-orchitis	14	8	5	1

Brucella epididymo-orchitis

These 14 patients were aged from 14 to 70 years (mean 31). They had more symptoms of general infection, including fatigue and muscular pain. In the majority, both epididymis and testis were involved; 3 presented with orchitis alone and 1 with epididymitis. Most patients had a high fever (>39°C) and 9 (64%) had symptoms of urinary tract infection. In 10 cases (71%) the leucocyte count ranged from 10,000 to 25,000/mm^3 and 11 (79%) showed disturbed liver enzymes, especially lactic dehydrogenase. Renal function tests were consistently normal, intravenous urography showing the presence of renal stones in 3 (21%).

Brucella agglutination titres ranged from 1:160 to 1:5120, correlating well with clinical severity. High titres (1280 and above) were obtained in 5 patients (36%), falling slowly after effective treatment. In only 2 cases (14%) was the diagnosis confirmed bacteriologically, *Br. melitensis* being isolated on blood culture.

Treatment was effective in 8 patients (57%), symptoms and local signs disappearing in 6 to 8 weeks. A secondary hydrocele persisted in 2 (14%) and enlargement of the epididymis in 3 (21%).

One patient underwent orchiectomy. He had presented with severe fever, a brucella agglutination titre of 1:1280 and a leucocyte count of 25,000/mm^3. A testicular abscess was suspected but on exploration no pus was found. After orchiectomy, performed because of secondary infection and sinus formation, histological examination showed the changes of granulomatous epididymo-orchitis.

Discussion

Brucellosis has a worldwide distribution (Matyas and Fujikura, 1984) and is especially common in the Middle East, Saudi Arabia and in neighbouring countries as well in Kuwait (Lulu *et al.*, 1988). Infection is usually acquired as a result of direct contact with infected animals or by consuming milk or cheese freshly made from them. The incidence of brucellosis is higher in rural than in urban communities: 38% compared with 8.8% in one survey (Talukdar *et al.*, 1984). Although only 2 or our 14 patients gave a clear history of drinking raw milk, 9 were from a sheep rearing region in the desert and had ready access to raw milk and its products.

The clinical and laboratory findings in brucellosis have been reviewed by Young (1983). In the present series we relied on the standard agglutination test to detect the presence of antibodies, but sensitivity tests for brucella IgG and IgM by radioimmunoassay and enzyme immunoassay are now increasingly available (Araj *et al.*, 1986). Although leucocytosis is not a typical feature (Crosby *et al.*, 1984), in 10 patients (71%) the white cell count exceeded 10,000/mm^3.

The disturbances in liver function tests may have been due to granulomatous brucella hepatitis with foci of necrosis. When serious liver dysfunction is found, however, intercurrent disease (schistosomiasis in some regions and chronic alcoholism in others) must always be excluded (Williams, 1987).

Estimates of the incidence of epididymo-orchitis in brucellosis have ranged from 2 to 14% (Christie, 1980), this infection as a cause of epididymo-orchitis being less likely to be overlooked in regions where it is known to be enzootic. The diagnosis was made in approximately one-third of the patients in this series. Treatment with tetracycline and streptomycin was effective in the majority but it should be emphasised that the regime now preferred is rifampicin 600 mg daily combined with doxycycline 200 mg daily for a minimum period of 6 weeks (Joint FAO/WHO Report, 1986).

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Acute Epididymitis: a Microbiological and Ultrasonographic Study

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Summary—in a prospective study of 24 men (mean age 28.3 years) with acute epididymitis who underwent epididymal aspiration, micro-organisms were detected in 15 (62.5%). *Chlamydia trachomatis* accounted for 10 (42%) of the cases, being located in both the urethra and epididymis in 5 individuals. Chlamydial serology supported the diagnosis of chlamydial infection, there being a strong correlation between the detection of *C. trachomatis* and elevated titres of both chlamydial IgG and IgM antibodies. In 4 patients (mean age 55.5 years), *Escherichia coli* was cultured from both mid-stream urine and epididymal aspirate. Transrectal ultrasound revealed abnormal prostatic scans in 19 patients (79%). These data confirm the aetiological role of *C. trachomatis*, support the notion that micro-organisms spread intra-canalicularly and suggest that the prostate is also involved in the inflammatory process in acute epididymitis.

Prior to the chlamydial serology studies undertaken just over a decade ago (Heap, 1975; Harnisch *et al.*, 1977), acute epididymitis was regarded mainly as idiopathic (Handley, 1946; Gartman, 1961). The serological data implied that *Chlamydia trachomatis* organisms (chlamydiae) played an active role and this was supported by isolation of chlamydiae directly from the epididymis in studies in the USA (Berger *et al.*, 1978, 1979, 1980) No further studies of this kind have been reported since then.

The involvement of the prostate in acute epididymitis has attracted little attention. However, in a recent study in which the Stamey localisation procedure (Meares and Stamey, 1968) was performed on a group of patients with acute epididymitis, chlamydiae were isolated from the expressed prostatic secretion of about 9% of the patients and other micro-organisms from about 10% (Grant *et al.*, 1987).

We report the findings of a prospective study of patients with acute epididymitis who were seen during an 18-month period (1987–88). They underwent epididymal aspiration to determine the aetiological infectious agents involved, and transrectal prostatic ultrasound in an attempt to assess the role of the prostate.

Patients and Methods

The study comprised 24 patients aged between 19 and 72 years (mean 28.3) who presented to the urology and genito-urinary medicine departments with a clinical diagnosis of acute epididymitis, All were seen within 5 days of the onset of symptoms, except for 1 patient who delayed consultation for 14 days, and none had received any antibiotics prior to the study.

The patients were investigated by urethral swabbing, mid-stream urine analysis, chlamydial serology, epididymal aspiration and transrectal prostatic ultrasound.

Two urethral swabs were taken from each patient, the first being tested for *Neisseria gonorrhoeae* (Gram stain and culture) and the second for chlamydiae (MicroTrak; Syva), *Mycoplasma hom-*

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inis organisms (mycoplasmas) and *Ureaplasma urealyticum* organisms (ureaplasmas) (culture). In the case of the latter swab, a smear was made first on the MicroTrak (Syva) slide before the swab was placed in mycoplasmal and ureaplasmal transport medium. A mid-stream specimen of urine was collected and tested for aerobic bacteria by routine microbiological methods.

Venous blood was drawn at initial presentation and 2 weeks later for chlamydial serology Serum IgG and IgM antibodies against *C. trachomatis* serovars A-K were sought by indirect immunofluorescence (Thomas *et al.*, 1976).

After these initial samples had been taken, epididymal aspiration was performed under regional anaesthesia, observing a strict aseptic technique (Berger *et al*, 1978). The groin and scrotum were cleansed with Hibitane and 10 ml of 1% lignocaine were instilled into the spermatic cord on the affected side. Once adequate anaesthesia had been achieved, as judged by applying gentle pressure on the epididymis, a further 2 ml of 1% lignocaine were injected into the scrotal skin overlying the most oedematous part of the epididymis. An 18-gauge needle was then inserted into the epididymis and 2 ml of sterile normal saline were injected before withdrawing approximately 1 ml of turbid fluid. This sample was subdivided; one portion was smeared on a MicroTrak (Syva)' slide for detection of chlamydiae, another placed in mycoplasmal and ureaplasmal transport medium and stored at −70°C prior to culture for these micro-organisms, another in Stuart's medium to be cultured for anaerobic bacteria and a fourth tested for aerobic bacteria by routine microbiological methods.

Each patient also underwent transrectal prostatic ultrasound using a Bruel and Kjaer 1846 machine with a 5.5 MHz transducer. This was performed in the left lateral position and the findings were recorded by means of hard copy.

After assessment the patients were treated with antibiotics and reviewed 2 weeks later At this time they were examined again clinically and a further mid-stream specimen of urine and a venous blood sample taken. However, a test cure for chlamydiae was not performed.

Results

Detection of micro-organisms in the urethra and epididymis

Micro-organisms were detected in 15 patients (62.5%). Chlamydiae were found in 10 patients (42%), being located in the urethra and epididymal aspirate in 5, in the epididymal aspirate alone in 2 and in the urethra alone in 3. In 2 patients (8%), ureaplasmas were detected in numbers $>10^4$, in the urethra and epididymis in 1 patient and in the urethra alone in the other. A further 4 patients were found to have ureaplasmas at a titre of 10^3 in the urethra alone and another 2 had mycoplasmas at a titre of 10^3, again in the urethra alone.

Aerobic bacteria were cultured from both the mid-stream urine and the epididymal aspirate of 5 patients: *Escherichia coli* was isolated from 4 and *Streptococcus faecalis* from 1. Two patients displayed mixed infections, chlamydiae and *E.coli* in one case and chlamydiae and ureaplasmas in the other. *N. gonorrhoeae* and anaerobes were not isolated from any patient.

Relation between age of patient and detection of micro-organisms

The mean age of chlamydia-positive patients was 26.7 years (range 20–34), that of culture-negative patients was 22.6 years (range 19–27) and that of *E.coli*-positive patients was 55.5 years (range 34–72). The difference between the former two groups and the latter group was significant ($P<0.001$).

Relation between detection of chlamydiae and chlamydial antibody

There was a strong correlation between the detection of chlamydiae and the occurrence of chlamydial IgG antibody (Table 1). Thus all patients who were chlamydia-positive had antibody titres of 1 : ⩾64, whereas those who were chlamydia-negative had titres of 1 : ⩽32, and most had titres of 1 : ⩽8. An antibody titre of 1 : 64 in 2 patients represented a 4-fold rise, but such a response was not seen in any of the other patients who exhibited titres of 1 : ⩾64.

A correlation also existed between the detection of chlamydiae and the occurrence of chlamydial IgM antibody (Table 2). Thus, of the 10 patients

Table 1 Relation between Detection of Chlamydiae and Chlamydial IgG Antibody

Detection of chlamydiae	*No of patients exhibiting an antibody titre (reciprocal) of*					
	⩽8	16	32	64	128	256 or >
Positive	—	—	—	3	2	5
Negative	10	3	1	—	—	—

The values represent the highest titre detected

Table 2 Relation between Detection of Chlamydiae and Chlamydial IgM Antibody

Detection of chlamydiae	*No. of patients exhibiting an antibody titre (reciprocal) of*						
	0	2	4	8	16	32	64
Positive	1	—	1	1	1	2	4
Negative	12	1	—	1	—	—	—

The values represent the highest titre detected.

who were chlamydia-positive, 7 had antibody titres of 1: ≥16, whereas none of the 14 chlamydia-negative patients had such titres, and 12 of these were without antibody. The 1 patient without IgM antibody but in whom chlamydiae were detected, in both the urethra and epididymal aspirate, presented for the first time 2 weeks after the onset of symptoms. In no case was a change in antibody titre observed between the first and second sample, except for a 2-fold decrease in titre in the sera of 1 patient.

Features of prostatic ultrasound

Nineteen patients (79%) had an abnormal prostatic ultrasound scan. Mid-range echoes (Fig. 1) were the most common feature; they were present in 18 cases (75%) and were located on the same side of the prostate as the affected epididymis in 12 (50%) and bilaterally in 6 (25%). High density echoes (Fig. 1) were noted in 15 cases (62%) and, when present in the region of the ejaculatory ducts (Fig. 2), were termed ejaculatory duct calcification; they occurred in 14 cases (58%). Dark, hypoechoic areas, termed echolucent zones, were present in 10 cases (42%). There was a relationship between these ultrasonic signs and the detection of micro-organisms (Table 3); a trend existed between the presence of abnormal features on ultrasound and positive cultures but failed to reach significance (0.5 > P > 0.1), probably because of the small numbers.

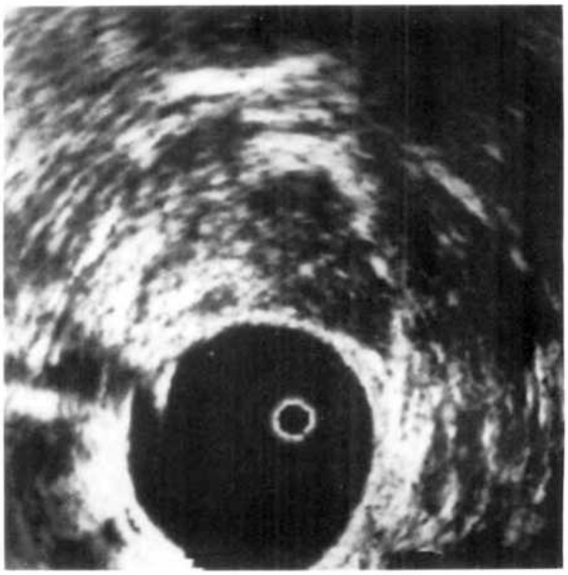

Fig. 1 Transrectal prostatic ultrasound scan. Mid-range and high density echoes in the peripheral zone.

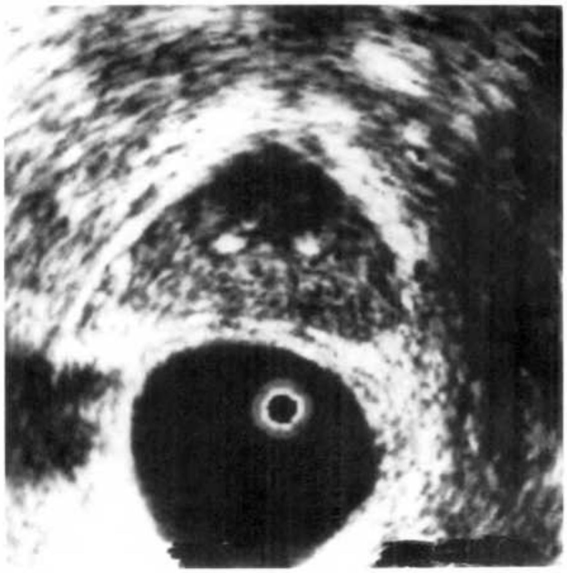

Fig. 2 Transrectal prostatic ultrasound scan. Bilateral ejaculatory duct echoes.

Discussion

This is the first study in which epididymal aspiration has been undertaken since that of Berger *et al.* (1980) in the USA. The results confirm that *C. trachomatis* is the major aetiological agent in acute epididymitis in young men (Grant *et al.*, 1987; Melekos and Asbach, 1987). The detection of chlamydiae in both the urethra and epididymal aspirate of half of the chlamydia-positive patients implies that the route of organism spread is intracanalicular. This supposition is supported further by the culture of *E. coli* and *S. faecalis* from both mid-stream urine and epididymal aspirate.

Despite the extensive microbiological survey, micro-organisms were not detected in 9 patients (37.5%). In one case, *U. urealyticum* was isolated

Table 3 Prostatic Ultrasound Findings in Relation to the Detection of Micro-organisms

	No (%) of patients with indicated ultrasonographic signs			
Micro-organism status	*Mid-range echoes*	*High density echoes*	*Ejaculatory duct echoes*	*Echolucent zones*
Positive	14 (58)	13 (54)	12 (50)	10 (42)
Negative	4 (17)	2 (8)	2 (8)	0

from both the urethra and epididymal aspirate, the first observation of this kind, yet it appears that neither this micro-organism nor *M. hominis* accounts for the shortfall in positive cultures. The serological data mentioned below do not suggest that any chlamydial infections were overlooked and it is possible that other micro-organisms, for example *M. genitalium*, might be responsible occasionally for apparently culture-negative cases. Two patients had mixed infections, which may result in poor response to treatment. In such cases epididymal aspiration may be of particular value.

The occurrence of chlamydial IgG antibody at a titre of 1 : ⩾64 and, to a lesser extent, IgM antibody at a titre of 1 : ⩾16 correlated with the detection of chlamydiae in the patients, although few were shown to have a rise in titre. On this basis it is tempting to suggest that reliance may be placed on serology alone to make a diagnosis of chlamydial infection. However, caution needs to be exercised because such antibody titres may sometimes be found in the sera of patients with uncomplicated non-gonococcal urethritis or in subjects without disease, particularly in a sexually active population. Serology, therefore, is best used as a means of supporting the diagnosis based mainly on attempts to detect chlamydiae in the appropriate secretions.

Transrectal ultrasound provides an objective assessment of the prostate, although the signs are not necessarily specific for any one disease (Rifkin, 1987). The study of benign prostatic disease has attracted little attention, but recent work has defined the ultrasonic features of prostatitis (Doble *et al.*, 1988; unpublished data). Mid-range echoes coincide with inflammatory features and/or fibrosis, and high density echoes with *corpora amylaceae* on histology (Doble *et al.*, 1988). Thus the finding of mid-range echoes in 75% of the patients in this study suggests that there may be a concomitant prostatic infection at the time of the epididymitis. There are conflicting data about the role of *C. trachomatis* in prostatitis (Mårdh *et al.*, 1978; Poletti *et al.*, 1985) and Doble *et al.* (1988) were unable to detect micro-organisms in biopsies taken under ultrasound control from the inflammatory areas of prostates of patients with abacterial prostatitis. However, this condition is chronic, so that the failure to detect micro-organisms is probably not in conflict with the concept of prostatic infection at the time of epididymitis, a condition which is acute. Nevertheless, assigning *C. trachomatis* to the prostate in acute epididymitis simply because it is detected in the expressed prostatic secretion of patients who also have a urethral infection is probably misguided, since urethral contamination of the secretion cannot be discounted (Grant *et al.*, 1987).

It is possible that some patients have a predisposition to the spread of micro-organisms as a result of previous damage. If the prostatic ultrasound findings in some cases reflect only fibrosis, it seems likely that the process causing such a pathological change must be long-standing. A possible causative factor is urinary reflux into the prostate and vas (Kirby *et al.*, 1982). This phenomenon may account for the high density echoes within the ejaculatory ducts of more than half of the patients studied. Of course, evidence of chronic changes in no way discounts the idea of prostatic infection associated with the acute epididymitis. Indeed, in view of the prostatic ultrasound findings suggestive of such an occurrence, we feel that antimicrobial therapy should be continued for 6 weeks to eliminate any prostatic infection. Furthermore, it is important to assess and treat any consorts of patients whose epididymitis is caused by sexually transmitted organisms.

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Effect of Phentolamine on Venous Return in Human Erection

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Summary—A group of 25 patients underwent Doppler penile blood examination and cavernometry before and after 5 mg of phentolamine injected intracavernously.

The organic or psychogenic nature of impotence was determined by psychological testing, the intracavernous injection of papaverine, hormonal evaluation, neurological examination, Doppler penile blood flow measurement and cavernometry for vascular investigations.

The intracavernous injection of phentolamine had no effect on the venous return and it provoked penile arterial dilatation. The erectile angle, which was also measured, was less evident than after the injection of papaverine.

The results confirmed the fact that an increase in arterial inflow alone is not sufficient to induce a rigid erection in man.

The intracavernous injection of drugs was first reported by Virag in 1982 as a means of provoking erection. By injecting papaverine, a non-specific muscle relaxant, into the penis he induced an erection in patients with normal vascular haemodynamics (Virag, 1982; Virag *et al.*, 1984). Brindley (1983) reported his experience in the diagnosis and treatment of impotence with the intracavernous injection of phentolamine or phenoxybenzamine, which have little in common except their blocking action, and he provoked erections in neurologically impotent patients. Since then many investigators have used these agents for the investigation of the normal physiology of erection and for the diagnosis and treatment of patients with impotence. We have compared the erections induced by papaverine and by phentolamine in patients with impotence and performed cavernometry before and after the injection of phentolamine in order to study the effect of these drugs on the mechanism of erection in men.

Patients and Methods

The series comprised 25 patients complaining of impotence for at least 6 months. Papaverine 60 mg was injected intracavernously with the patient in the standing position and pinching the base of the penis. The erectile angle between the position of the penis and the legs was measured 10 min after the injection. The penile rigidity was assessed by manual palpation (Wespes *et al.*, 1987). The patients underwent hormonal, neurological and vascular examinations 1 week later. Serum testosterone and prolactin levels were measured. The neurological status was assessed by measuring the latency of the bulbocavernous reflex (Siroky *et al.*, 1979). Vascular assessments consisted of a Doppler examination of the penile arteries with recording pulse waves and measurement of the penile brachial index (Sonicaid-Vasoscan) and cavernometry (Bellco pump) to exclude arterial or venous diseases (Wespes *et al.*, 1984). When the erectile flow was measured the intracavernous needle was disconnected from the pump and the penis emptied until the flaccid state was obtained. The shaft of the flaccid penis was then pressed several times to evacuate the remaining physiological saline; 10 min after these procedures, 5 mg of phentolamine were injected intracavernously and the base of the penis compressed manually as described previously.

After 10 min the erectile angle was measured and a second Doppler examination and cavernometry were performed to evaluate the role of the vasoac-

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tive drug on the two vascular components. All of these studies were performed with the patient in the standing position.

Analysis of the results was conducted according to the two-way analysis of variance, blocks representing individuals and treatment groups (control) and experimental papaverine and phentolamine administration) (Snedecor, 1956).

Results

Five patients presented an erectile angle > 90° (90–125°, mean 100) with satisfactory rigidity after the injection of papaverine and were considered to have no significant vascular disorders. Doppler studies were normal and cavernometry showed the normal flow necessary to provoke an erection in the range of 100 to 120 ml/min (mean 110). Hormonal results and neurological examinations were also normal. The patients were therefore judged to have psychogenic impotence, which had been suspected from their psychological screening.

In 20 patients an erectile angle <90° (10–70°, mean 37) was noted without penile rigidity after the injection of papaverine. They were therefore thought to have vascular abnormalities and hence organic impotence. Doppler examination revealed normal arteries in 8 patients and an abnormal supply in the remaining 12 (PBI<0.7). Nine patients had a normal erectile flow to induce an erection, ranging from 100 to 130 ml/min (mean 118); 11 patients required a higher flow to provoke an erection, ranging between 180 and 230 ml/min (mean 198) and were thought to have venous leakage. None had hormonal or neurological dysfunction.

After the injection of phentolamine, the 5 psychogenically impotent patients presented an erectile angle significantly less than the one obtained with papaverine (t=25, $P<0.001$). The organically impotent patients also showed an inferior erectile angle. The difference was less marked but remained significant (t=5, $P<0.001$) (Table 1). The amplitude of the arterial pulse waves demonstrated an increase in most cases but this was less marked when the arteries were abnormal. The erectile flow during dynamic cavernometry was not modified after the injection of phentolamine (Table 2). All patients with venous leakage felt discomfort because of hypotension as a systemic side effect of phentolamine. After removal of the catheters, a compressive dressing was applied to avoid penile oedema or haematoma. The patients were kept under observation for 2 h. No priapism or serious complications were observed. The patients with hypotension were treated with bedrest until their blood pressure returned to normal.

Table 1 Comparison of Erections Induced by Papaverine and Phentolamine in Patients with Psychogenic and Organic Impotence

	Erectile angle between penis and legs (patients in standing position)	
No of patients	*With papaverine*	*With phentolamine*
5 without vascular disorders	100° (90–125)	35° (20–50)*
20 with vascular disorders	37° (10–70)	18° (0–30)†

* (t=25, $P<0.001$). † (t=5, $P<0.001$)

Table 2 Results of Cavernometry Without and With Phentolamine

	Erectile flow to induce erection (ml/min)	
No of patients	*Without phentolamine*	*With phentolamine*
5 with psychogenic impotence	110 (100–120)	110
9 without venous leak	118 (100–130)	115
11 with venous leak	198 (180–230)	190

Discussion

Cavernometry is a useful technique to diagnose a venous problem in the assessment of patients with organic impotence (Wespes *et al.*, 1984). This test is not physiological because it does not take into account the role of the arterial component on venous return during erection. Cavernometry with the intracavernous injection of papaverine seems to be more physiological (Virag *et al.*, 1984; Wespes *et al.*, 1986). It can demonstrate an important reduction in the erectile flow required both to create and maintain erection in psychogenically impotent patients and in organically impotent patients without venous leakage (Wespes *et al.*, 1986). In patients with venous leakage, the erectile flow also decreases but remains higher than in the first two groups (Wespes *et al.*, 1986). The pathological venous drainage responsible for the caverno-venous leakage is visualised on cavernography if an erection is induced by a high infusion rate and increased maintenance flow rate.

Juenemann *et al.* (1986b) investigated the haemodynamic changes in the canine corpora cavernosa by intracavernous papaverine or phentolamine injection, after occlusion of the aorta. They showed that the venous outflow was reduced after the papaverine injection but observed no modifications after phentolamine. In the present study, phentolamine had no effect on the venous return, although it provoked an increase in the arterial inflow. The erections were of poorer quality with phentolamine than with papaverine. In patients considered psychogenic with the papaverine test, we observe no rigid erections following the injection of phentolamine. These patients with normal vascular components should respond in the same way as normal potent men. The dose of phentolamine was identical to that used by Brindley (1983) and Blum *et al.* (1985), who obtained rigid erections in normal patients. The action of the drug may be less pronounced after cavernometry, as we had already observed it to be with papaverine (Wespes *et al.*, 1986). For this reason we waited 10 min after the first cavernometry before injecting phentolamine. Emptying the corpora through the intracavernous needle and massage of the flaccid penis allows a better recovery of penile haemodynamics.

The base of the penis is pinched while injecting phentolamine and this ensures local distribution of the drug and avoids its rapid elimination into the systemic circulation. We did not use a tourniquet because this could stop the arterial inflow. The improvement in penile arterial pulse waves demonstrated the effective local action of the drug.

It is possible that phentolamine acts more effectively on the arterial smooth muscles than on the corporeal smooth muscles, which have different alpha-receptor subtypes (Hedlund and Anderson, 1985). The increase in arterial inflow is not sufficient, however, to raise the intracorporeal pressure high enough to reduce the venous outflow. In addition to its effect on arterial smooth muscle, papaverine has a specific action on the venous system which may explain the improved erection and lower erectile flow seen during cavernometry regardless of the arterial supply (Juenemann *et al.*, 1986a; Delcour *et al.*, 1987). Our series was small, for we abandoned it after studying 25 patients because of the immediate secondary effects of the drug in patients with venous leakage. We had already observed this problem with papaverine, though less frequently (Wespes and Schulman, 1988).

If the treatment of impotent patients with higher doses of phentolamine or papaverine is considered, we advise that venous leakage should be excluded because of the risk of provoking discomfort with hypotension. Ligation of the venous return then allows a better trapping of arterial blood into the penis and reduces the dose of the vasoactive drug injected into the penis (Wespes and Schulman, 1988).

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Case Reports

Early Calcification of Haematoma in the Renal Pelvis

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Case Report

A 47-year-old female presented with left-sided loin pain. Initial intravenous urography (IVU) showed a stone impacted in the left pelviureteric junction. A small left lower pole caliceal calculus had been noted 6 years previously.

In view of the obstruction an attempt was made to drain the system percutaneously. This was not successful and produced bleeding into the collecting system. An attempt was then made to remove the stone ureteroscopically, but this too failed and resulted in mid and distal ureteric oedema. Because of this and the continuing presence of the stone a double pigtail stent was positioned in the ureter. During the next 2 weeks the stone passed spontaneously. IVUs showed clot in the collecting system to persist and there was also initially a small urinoma. The ureteric stent was removed after 6 weeks.

By 4 months the clot in the collecting system was shown to be calcified around its margins (Fig. 1). In view of the persistence of the clot and its calcification it was removed percutaneously in pieces, using a nephroscope through a 26 F tract (Fig. 2). A subsequent IVU was normal. Uric acid, calcium and phosphate levels were normal throughout, both in the blood and urine, and all urine cultures were negative.

Comment

Two aspects of the case are of interest: failure of the clot to dissolve in the presence of normal urine and the rapidity of calcification of the intrapelvicaliceal clot. Although the patient was a known stone former, all metabolic tests were normal and the urine was sterile throughout. Only one previous report has demonstrated such rapid calcification of clot (Valvo *et al*., 1983), occurring in a 17-year-old male 4 months after a road traffic accident. Calcification has also been reported following renal biopsy (1 case) (Fletcher and McGregor, 1979), nephrolithotomy (5) and idiopathic (2) (Thomas *et al*., 1976).

The constituents of the calculi in all previous cases were calcium urate and oxalate. The calculus in this case had traces of ammonium and phosphate in addition.

There is no apparent unifying factor in these cases. This report illustrates a rare and unpredicta-

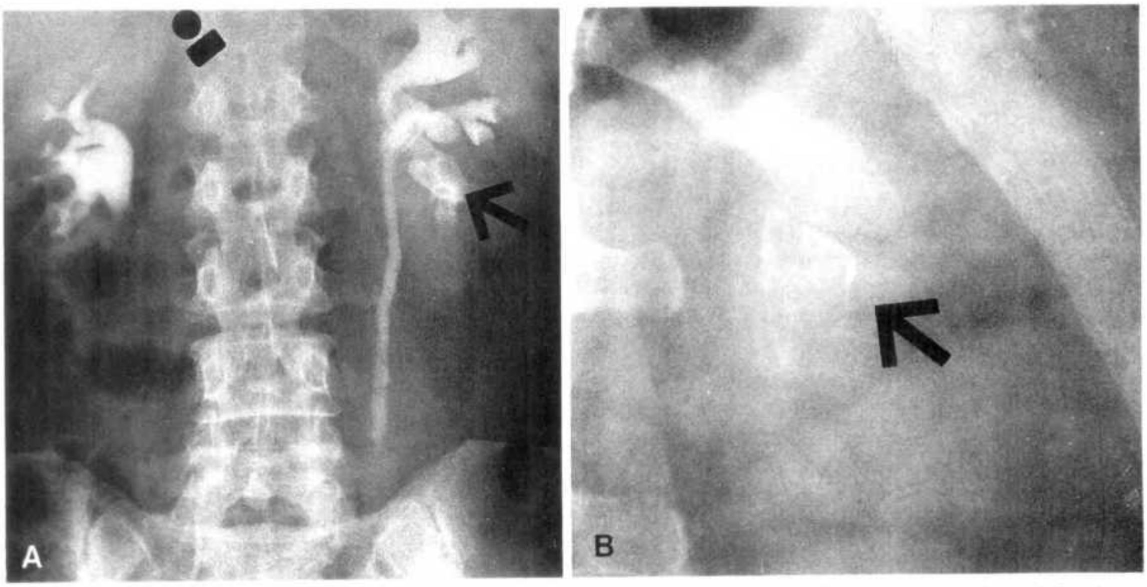

Fig. 1 (A) IVU 8 weeks after nephrostomy and 2 weeks following removal of the double pigtail stent, showing filling defect (arrow) in the left pelvicaliceal system. (B) Coned view of left kidney from KUB taken 3 months after IVU in Fig. 1A. There is marginal calcification around the filling defect in the left pelvicaliceal system.

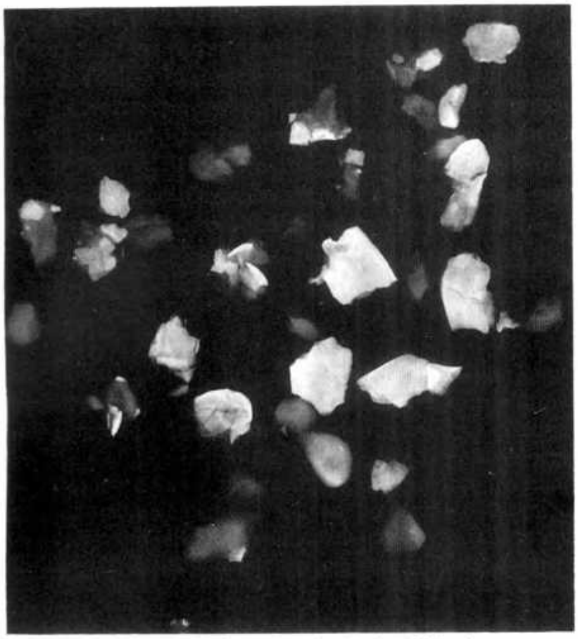

Fig. 2 Radiograph of fragmented calculus following percutaneous nephrolithotomy from left pelvicaliceal system.

ble sequel to intrapelvicaliceal haematoma formation.

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Renal Parenchymal Malakoplakia

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Case Report

A 27-year-old female presented with a 3-month history of right loin pain and fever; for 1 month she had noticed a vague mass in the right flank. Physical examination revealed a firm, non-tender, ballotable right renal mass.

Routine investigations were within normal limits except for *Escherichia coli* in the urine. IVU revealed a non-functioning right kidney with a normal left one. Ultrasound confirmed the presence of a solid right renal mass which was avascular on renal angiography. A right nephrectomy was performed.

The patient made an uneventful recovery. Histopathology revealed destroyed renal parenchyma and chronic inflammatory exudate with histiocytes. Large numbers of intracytoplasmic Michaelis-Gutmann bodies were observed (Fig.), confirming the diagnosis of renal malakoplakia.

Comment

Malakoplakia is a granulomatous disease with a predilection for the genitourinary system and was first described by Michaelis and Gutmann in 1902. Since then 200 cases have been reported, of which renal parenchymal malakoplakia accounts for only 16% (Stanton and Maxted, 1981). The underlying abnormality is defective phagocytosis as a result of a low GMP/AMP ratio, leading to malfunction of the intracellular tubules. Improperly digested bacteria become mineralised, leading to the formation of the diagnostic Michaelis-Gutmann bodies (Curran, 1987). It has a strong correlation with coliform infection.

Although antibiotics, ascorbic acid and a cholinergic agonist have been recommended for vesical

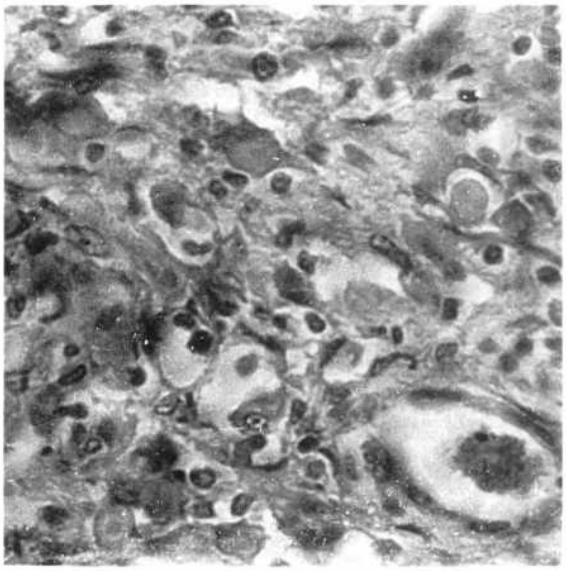

Fig. Inflammatory reaction consisting mostly of histiocytes with intracytoplasmic Michaelis-Gutmann bodies.

malakoplakia, for unilateral renal malakoplakia nephrectomy is the choice (Deridder *et al.*, 1977).

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Renal Hydatid Disease. Importance of Pre-operative Diagnosis

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Case Report

A 63-year-old female from rural India, whilst under investigation for pulmonary tuberculosis, was found to have a tender right-sided abdominal mass. This had caused increasing discomfort for at least 20 years. Urinary symptoms were absent. Serum urea and electrolytes and full blood count were normal; plasma viscosity was slightly elevated. Plain abdominal X-rays and isotope liver/spleen scan showed the mass to be below the right lobe of the liver, which it compressed. Intravenous urography exhibited medial displacement of the right renal pelvis and abdominal ultrasound disclosed the cystic structure of the mass. Arteriography confirmed a renal origin but its nature remained uncertain. Urine cytology was negative. At laparotomy a unilateral cystic mass (16 × 15 × 12 cm) was found arising from the right kidney. Partial aspiration of the cyst contents facilitated the total nephrectomy which was performed. On incision, this had the classical appearances of a hydatid cyst (Fig. 1), containing over 40 daughter cysts and yellow/grey hydatid sand. Histologically, all daughter cysts had inner germinal layers producing large numbers of scolices of *Echinococcus granulosus* (Fig. 2). This had therefore been a considerable infectious risk. Post-operative recovery was uneventful, with investigations for pulmonary tuberculosis proving negative. The results of serology on blood obtained pre-operatively were equivocal; by ELISA, hydatid antibodies were positive, but negative by CFT. No history of contact with dogs and/or sheep was obtained.

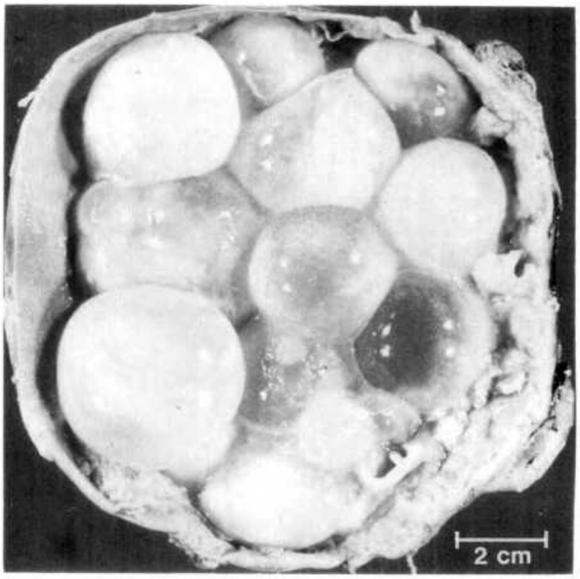

Fig. 1 Renal hydatid cyst containing numerous daughter cysts.

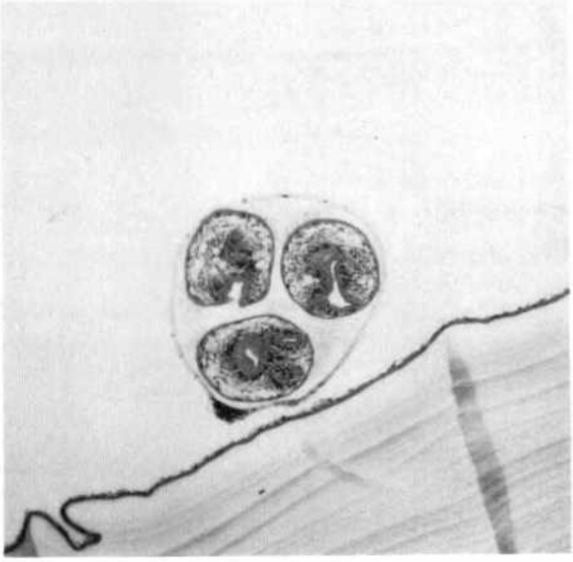

Fig. 2 Scolices of *Echinococcus granulosus* within daughter cysts. (H and E × 160).

Comment

Although rare in the UK, comprising 2 to 3% of all cases, renal hydatid disease caused by *E. granulosus* should be considered in the differential diagnosis of a cystic renal mass. Usually asymptomatic for many years, it often presents with a mass (Aragona *et al.*, 1984), although seldom as large as described here. Useful investigations include pyelography, ultrasound scan and angiography, but CT scan is claimed to allow for definitive diagnosis (Petrillo *et al.*, 1981). Serology may produce false negative results. Pre-operative diagnosis is important as scolicidal agents may be introduced during surgery, thereby reducing the risk of dissemination of hydatid infection. Surgery is invariably required since the role of drug therapy with mebendazole is uncertain (British Medical Journal, 1979). Cyst puncture with aspiration of fluid, whilst helpful in establishing the diagnosis (Roylance *et al.*, 1973) should be avoided as this may cause acute anaphylaxis.

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Primary Osteogenic Sarcoma of the Kidney

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A case of primary osteogenic sarcoma of the kidney is presented which highlights the clinical features and extremely poor prognosis of this rare neoplasm. Only 11 cases have been reported previously in the literature.

Case Report

In November 1985 a 56-year-old man presented with a 1-day history of right flank pain and gross haematuria. Examination was unremarkable except for some tenderness in the right flank. A plain abdominal X-ray showed a circular rim of calcification overlying the right renal shadow. Intravenous urography confirmed that the calcification was associated with a mass in the lower pole of the right kidney. A CT scan of the abdomen confirmed a solid, partly calcified mass in the right kidney without apparent local spread (Fig. 1). A chest X-ray and bone scan were both normal. A provisional diagnosis of carcinoma of the kidney was made and a right radical nephrectomy was performed 1 week after presentation.

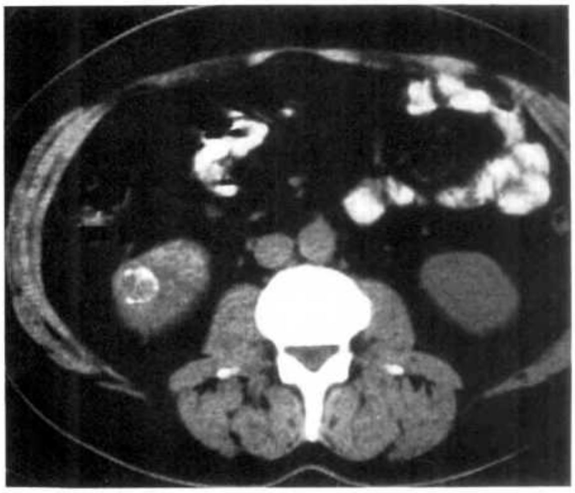

Fig. 1 CT scan showing peripheral calcification of the right renal tumour.

Pathology revealed a 4-cm, partly calcified tumour in the lower pole of the kidney with extension into the renal vein and through the capsule into perinephric fat. The tumour consisted largely of spindle-shaped and polygonal cells with much malignant osteoid present. The histological appearances were those of osteogenic sarcoma.

A CT scan of the chest 7 months post-operatively showed multiple metastases in the lung, some of which were calcified (Fig. 2). A repeat bone scan was negative. The patient received combination chemotherapy of cyclophosphamide, vincristine, Adriamycin and DTIC, but the lung metastases progressed radiographically. A

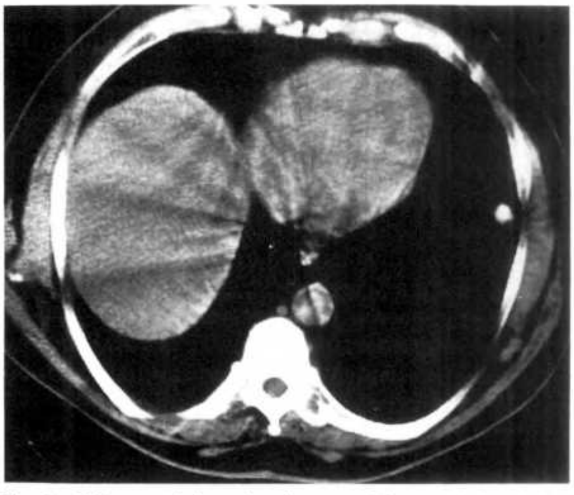

Fig. 2 CT scan of chest showing one of the multiple calcified pulmonary metastases. It is seen in the periphery of the left lung with a density similar to that of the adjacent ribs.

course of cisplatin was then administered without objective response.

In March 1987, 16 months after nephrectomy, he developed a skin lump on the left side of the neck. This was excised and histology revealed a nodule measuring 17×13 mm in the subcutaneous fat. The cells were predominantly spindle-shaped with frequent mitoses. Several areas of dense osteoid were present. The appearances were those of osteogenic sarcoma consistent with metastasis from the renal lesion

A month later he developed a mass in the right upper abdomen. Ultrasound confirmed a mass which appeared to be intraperitoneal in the right upper quadrant and also demonstrated a solid mass in the left lobe of the liver. His condition deteriorated until death in May 1987, 18 months after presentation. An autopsy was not performed.

Comment

Including this report 12 cases of primary osteogenic sarcoma of the kidney have now been reported. The tumour has occurred in patients ranging in age from 29 to 82 years. There is no apparent predilection for side (6 left, 6 right) or gender (7 male, 5 female).

Dense calcification of the renal primary is usually seen on plain abdominal X-ray but peripheral calcification, as in the case reported, has also been described. Metastases often show osteoid and bone formation (Axelrod *et al.*, 1978). Metastatic spread is usually to lungs and liver but spread to unusual sites such as the vulva (Soto *et al.*, 1965) and (in this case) skin has occurred.

A review of the 12 cases reveals a very poor prognosis for primary osteogenic sarcoma of the kidney. The first reported case was a post mortem diagnosis; 9 of the remaining 11 patients died within 1 year of diagnosis, our patient survived for 18 months and 1 was disease-free 3 years after nephrectomy. This last case was unusual in that the tumour was a synchronous renal carcinoma and osteogenic sarcoma (Moon *et al.*, 1983).

An obvious reason for the poor survival figures is the late stage of disease at diagnosis. Four patients had metastases at diagnosis, 3 tumours were invading adjacent organs and 4 were invading either the renal vein or through the renal capsule. The only patient still alive at the time of its reporting was the one with a tumour confined to the kidney.

Even though the number of cases available for assessment is small, there is little to suggest that this tumour is responsive to chemotherapy or radiotherapy.

Two patients received combination chemotherapy comprising vincristine, methotrexate and Adriamycin, but 1 died 1 month and the other 6 months after therapy. One patient received Adriamycin and cyclophosphamide but died 4 months later. Our patient received vincristine, Adriamycin, cyclophosphamide and DTIC with no evidence of response or remission, nor was there any response to cisplatin.

The 1 patient treated with external beam radiotherapy died 1 month later.

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Spontaneous Regression of Subcutaneous and Pulmonary Metastases from Renal Carcinoma

P. J. THOMAS, M. STOTT and G. T. ROYLE, *Surgical Unit, Royal South Hants Hospital, Southampton*

Case Report

A 74-year-old man presented in October 1984 with a 5-cm ulcerated lesion on the scalp over the occiput. Incision biopsy showed metastatic adenocarcinoma consistent with a renal primary Investigation by chest X-ray, IVU, ultrasound and angiography showed a left renal tumour with pulmonary metastases in the left upper and mid-zones. There was no evidence of liver or osseous metastases. He received a palliative course of radiotherapy (24 Gy over 6 days) and underwent left nephrectomy in December 1984. Histological examination confirmed a renal carcinoma confined within the renal capsule but extending into the renal vein. The patient made a rapid recovery from the operation. His general health improved dramatically with total resolution of the scalp metastases and chest symptoms. He has remained well on follow-up to June 1987 and has gained 2 stone in weight. The chest X-ray appearances improved slowly, with apparent total regression of the metastases by January 1987 (Figs 1 and 2), maintained in June 1987.

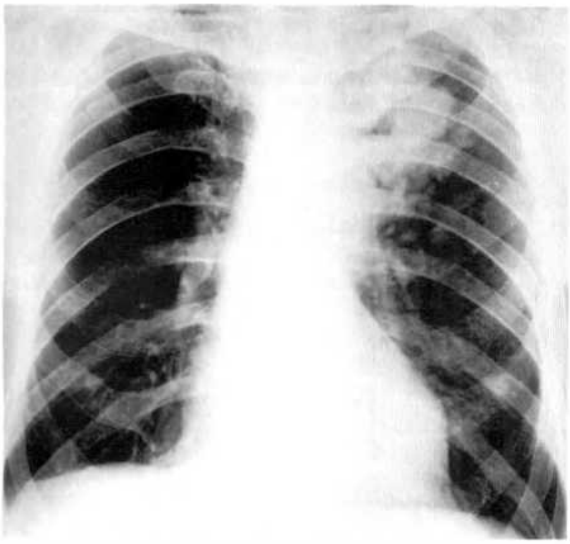

Fig. 1 Pre-operative chest X-ray (November 1984) showing left upper and mid-zone metastases.

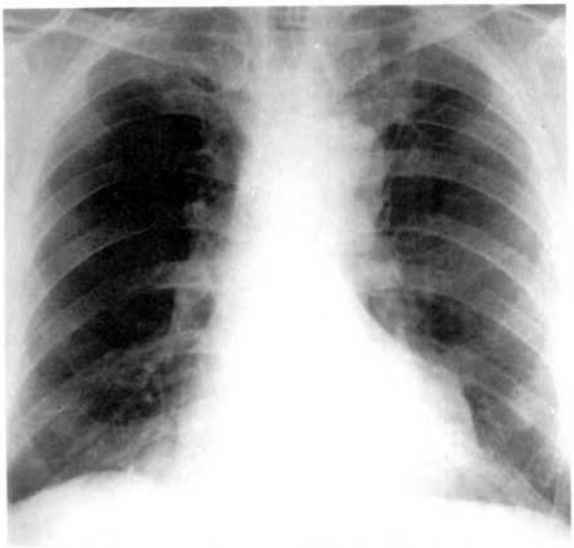

Fig. 2 Chest X-ray (January 1987) showing no evidence of metastases.

Comment

The phenomenon of spontaneous regression of metastases from renal carcinoma is now more widely accepted (Kirk, 1987), but reports of this event are still uncommon and definite histological evidence of metastatic disease was available in less than half of the 67 documented cases reviewed by Fairlamb (1981). Pulmonary metastases appear to have the highest incidence of spontaneous regression, accounting for 60 of the 67 cases reported by Fairlamb. This series also included the only previous report of spontaneous regression of pulmonary metastases following nephrectomy and radiotherapy to non-pulmonary metastases. Nephrectomy and other treatment modalities in the face of widespread metastatic disease remain controversial (Kirk, 1987). Our patient illustrates that a worthwhile period of relief may be obtained in an apparently hopeless situation.

References

Fairlamb, D. J. (1981). Spontaneous regression of metastases of renal cancer. *Cancer*, **47**, 2102–2106.

Kirk, D. (1987). Spontaneous regression of metastatic renal carcinoma. *Br. J. Surg.*, **74**, 1–2.

Requests for reprints to: G.T. Royle, Professorial Surgical Unit, Royal South Hants Hospital, Graham Road, Southampton SO9 4PE.

Extra-mammary Paget's Disease of the Penis

I. L. JENKINS, *Department of Urology* and B. CONROY, *Department of Histopathology, Royal Naval Hospital, Haslar, Gosport*

Case Report

A previously healthy, 45-year-old male presented in 1983 with superficially invasive transitional cell carcinoma of the bladder (grade II). There was no dissemination and he underwent fractionated radical radiotherapy (6000 cGy). This was complicated by severe radiation cystitis and resulted in a scarred, small capacity bladder.

Follow-up revealed no evidence of recurrent or disseminated disease until 3 years later, when cystoscopy demonstrated areas of sloughing epithelium which were resected. These exhibited features of radiation change, but some contained recurrent transitional cell carcinoma. Investigation failed to identify metastases and he was prepared for salvage cystectomy. At that time a 4-cm, non-tender, red, granular area involving the epithelium around the urethral meatus and of 2 months' alleged duration was found (Fig. 1). Biopsy showed extensive infiltration of the squamous epithelium by large pleomorphic cells with pale and foamy PAS-positive cytoplasm. The appearances were those of penile extra-mammary Paget's disease (Fig. 2A).

Cystourethrectomy with circumferential excision of the glans in continuity and ileal diversion were performed. Histological examination of the resected specimen showed recurrent invasive transitional cell carcinoma of the bladder (grade III). In addition, surrounding the

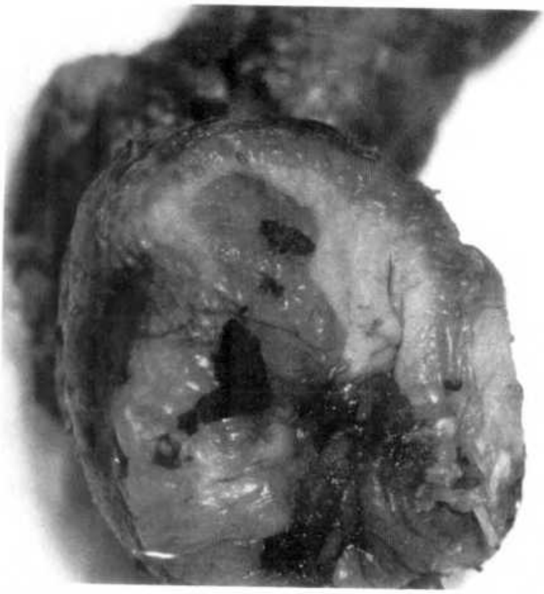

Fig. 1 Close-up of glans removed in continuity with urethra. The peri-meatal epithelium is granular and focally haemorrhagic.

proximal urethra was a well differentiated adenocarcinoma arising in a peri-urethral gland and superficially invading the corpus spongiosum (Fig. 2B). Sections from the glans and the penile urethra confirmed widespread pagetoid invasion.

Six months later he rapidly became cachetic with cervical node, liver and bone metastases. His condition was considered terminal and lymph node biopsy, though of academic interest, was not justified. He died shortly afterwards and no autopsy was performed.

Comment

Extra-mammary Paget's disease is rare and is usually related to an underlying apocrine adenocarcinoma.

Involvement of the glans has been recorded in only 6 cases (Tomaszevski *et al.*, 1986), all associated with urothelial carcinoma. One was related to a primary distal urethral carcinoma and the others were in patients aged 51 to 81 years (mean 69) arising 5 months to 7 years (mean 41 months) after radical treatment for proven transitional cell carcinoma of the bladder.

This case is, we believe, the first to recognise extra-mammary Paget's disease of the glans not related to primary urothelial disease but to an underlying adenocarcinoma of a peri-urethral gland.

References

Tomaszevski, J. E., Korat, O. C., Livolsi, V. A. *et al.* (1986). Paget's disease of the urethral meatus following transitional cell carcinoma of the bladder. *J. Urol.*, **135**, 368–370.

Requests for reprints to: Surgeon Commander I. L. Jenkins, RN, Department of Urology, Royal Naval Hospital, Haslar, Gosport PO12 2AA.

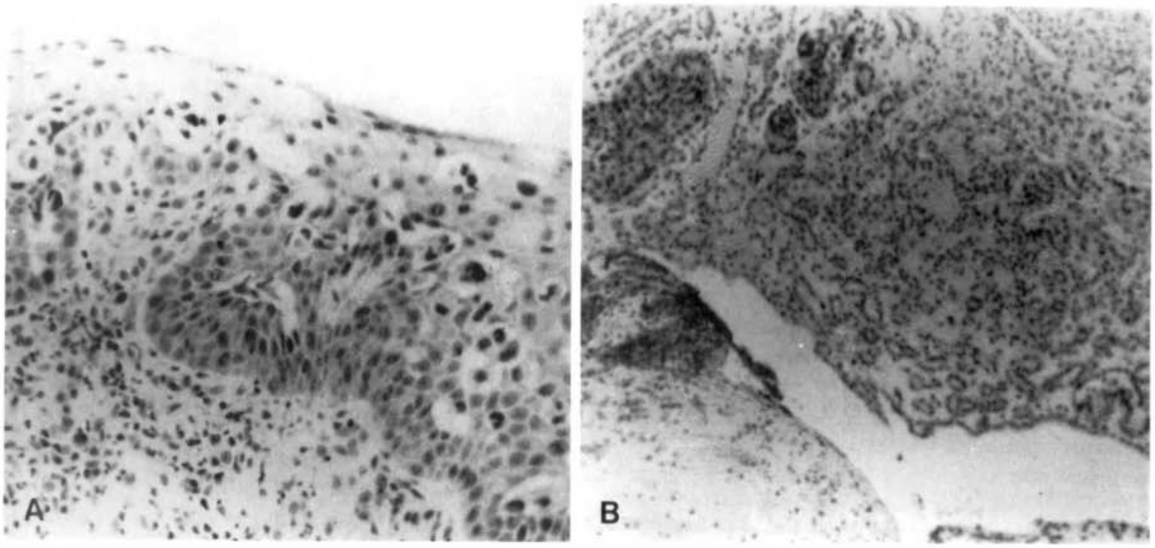

Fig. 2 (A) Detail of initial biopsy of glans showing pleomorphic pale pagetoid adenocarcinoma cells within the squamous epithelium. (H and E × 200). (B) Histological section of the well differentiated adenocarcinoma arising from a proximal periurethral gland. The urethral lumen is seen in the lower half of the field (H and E × 80).

Another Approach to the Treatment of Priapism

L. FORSBERG and A. M. OLSSON, *Departments of Diagnostic Radiology and Urology, University Hospital, Lund, Sweden*

After giving more than 200 intracorporeal injections of dibenylene for both diagnostic (Ekelund *et al.*, 1988) and therapeutic indications, we report 1 patient who developed priapism.

Case Report

A 63-year-old man who presented with a 2-year history of impotence appeared to have a subnormal penile arterial blood flow. The penile-brachial blood pressure difference was more than 30 mm Hg (Forsberg *et al.*, 1982). An angiogram, performed after the intracorporeal injection of dibenylene, demonstrated occlusion of both right and left pudendal arteries and two thin penile arteries were filled by collaterals from the left obturator artery (Fig.). The following day, when leaving hospital, the patient reported that he was very pleased with the previous day's treatment, for he still had an erection. He went home to see his wife and 6 h later reported that he still had an erection but the penis had started aching. Within an hour he was back in hospital. It was then 30 h since the dibenylene had been injected into the corpora. The corpora were stiff and there was no doubt that the patient had developed priapism. To relieve his pain and discomfort a penile block was performed with 10 ml of 1% Carbocain without adrenaline. In order to carry out a pelvic steal test (Michal and Kramar, 1978; Goldstein *et al.*, 1982) the patient was instructed to run down the stairs to the basement and up again to the ninth floor—twice. Following this exertion the stiffness had lessened and after another two visits to the basement the penis was small and flaccid, as it usually is after hard physical training. He has had no further erection and is on the waiting list for a penile implant.

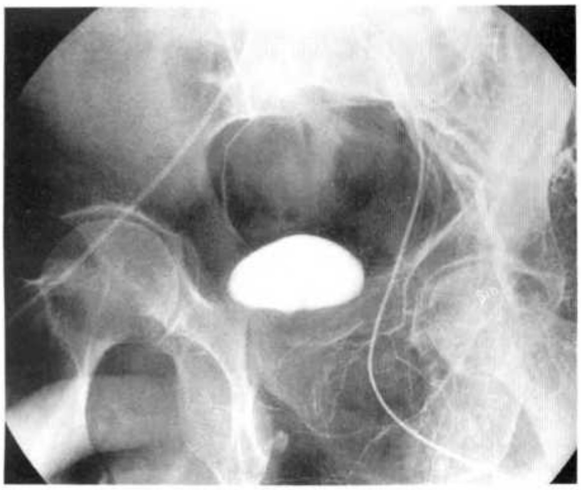

Fig. Selective contrast injection into the left hypogastric artery. Distal occlusion of the left pudendal artery. The thin penile vessels are filled from collaterals of the left obturator artery.

Comment

The development of priapism after pharmacoerectile therapy is a well-known phenomenon, but it seems remarkable that it can occur in a man with such a poor penile blood supply. Iatrogenic priapism is probably diagnosed much earlier than the spontaneous form and it is probably easier to cure. The local pain, which develops in the late stages of priapism, usually brings the patient to hospital and tends to make him inactive. When this pain has been relieved the patient can be prescribed physical exercise.

References

Ekelund, L., Forsberg, L. and Olsson, A. M. (1988). Pharmacoangiographic assessment of penile arteries in patients with erectile failure. *Urology*, **XXXI**, 271–274.

Forsberg, L., Olsson, A. M. and Neglen, P. (1982). Erectile function before and after aorto-iliac reconstruction: a comparison between measurements of Doppler acceleration ratio, blood pressure and angiography. *J. Urol.*, **127**, 379–383.

Goldstein, I., Sikory, M. B., Nath, R. L. *et al.* (1982). Vasculogenic impotence: role of the pelvic steal test. *J. Urol.*, **128**, 300–306.

Michal, V. and Kramar, R. (1978). External iliac "steal syndrome". *J. Cardiovasc. Surg.*, **19**, 355–358.

Requests for reprints to: A.M. Olsson, Department of Urology, University Hospital, S-221 85 Lund, Sweden.

British Journal of Urology (1989), 63, 106
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Point of Technique

Ureteric Meatotomy Guided by Antegrade Insertion of a Double J Splint

G COOKSEY, A. M. DEANE, A. THOMAS and M HANDLEY ASHKEN, *Departments of Urology and Radiology, Norfolk and Norwich Hospital, Norwich*

Narrowing of the ureteric orifices is commonly associated with post-radiation fibrosis and the bladder neck stenosis which may occur after transurethral prostatectomy. Endoscopic resection of the narrowed orifice to open the lumen of the dilated intramural ureter is a successful method of treatment and a simple alternative to reimplantation, which may be technically difficult in post-radiation cases. Occasionally we have experienced difficulties in visualising the affected ureteric orifices at cystoscopy when attempting this procedure. The following technique has been successfully used to overcome this problem.

Technique

A double J stent is inserted antegradely into the ureter using a standard technique under local anaesthesia (Mazer *et al.*, 1979). In brief, percutaneous puncture of the dilated pelivicaliceal system is performed and a floppy tipped guide wire is negotiated through the pelviureteric junction, down the ureter and into the bladder with the aid of fluoroscopic screening. A size 5F double J ureteric stent (William Cook) is then advanced over the guide wire. The position of the stent is checked and the guide wire is withdrawn.

The following day (or when any haematuria has cleared), transurethral endoscopy is undertaken. Using a Collings diathermy knife, the stenosed ureteric orifice is incised using the double J stent as a guide, care being taken to avoid direct contact between the diathermy knife and the stent in case of breakage. The meatotomy is complete when an adequate opening in the dilated proximal part of the intramural ureter can be seen. The double J stent can be removed immediately via the cystoscope using biopsy forceps.

To date, 3 patients have been treated using this technique and all have successful long-term results.

One note of caution. We strongly advise against using diathermy near metallic guide wires, which may disintegrate on application of the electrical current.

Reference

Mazer, M. J., LeVeen, R. F., Call, J. E. *et al.* (1979). Permanent percutaneous antegrade ureteral stent placement without transurethral assistance *Urology*, **14**, 413–419

Requests for reprints to G Cooksey, Department of Urology, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW

British Journal of Urology (1989), 63, 107–108

Notices

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President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes' duration.

Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

International Consensus Conference on Prostate and Testicular Cancer

Hull. 12–15 April 1989

Further information from: D. W. W. Newling, 21 Albion Street, Hull HU1 3TG.

International Symposium on Genital Papillomavirus Infections: Advances in Modern Diagnosis and Therapy

Hamburg, West Germany. 3–5 February 1989

Further information from: Dr G. Gross, Department of Dermatology, University Hospital Hamburg-Eppendorf, Martinstrasse 52, D-2000 Hamburg 20, West Germany.

International Symposium on Adult and Paediatric Genitourinary Reconstructive Surgery

New Delhi and Jaipur, India. 16–21 February 1989

Further information from: Dr U. B. Patil, Department of Urology, SUNY Health Science Center, Syracuse, New York 13210, USA.

Urological Society of Australasia. 42nd Annual Meeting

Melbourne, Australia. 2–7 March 1989

Further information from: Secretary, Urological Society of Australasia, 145 Macquarie Street, Sydney, NSW 2000, Australia.

International Symposium on Dysfunction of the Lower Urinary Tract: Present Achievements and Future Perspectives

Nijmegen, The Netherlands. 3–4 March 1989

Further information from: Miss Marion van Beckhoven, c/o Department of Urology, Radboud University Hospital, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Ghent's Urethral Surgery Day

Ghent, Belgium. 14 April 1989

Live demonstrations will be given of urethral reconstructive surgery (hypospadias, strictures, etc).

Further information from: Professor W. A. De Sy, Department of Urology, University Hospital, 9000 Ghent, Belgium.

Seventh International Symposium of Radionuclides in Nephro-urology

Williamsburg, USA. 7–10 May 1989

Topics for discussion include hypertension, renal physiology, radiopharmaceuticals, renal function, renal imaging, metabolic disease, transplantation, paediatrics and urological diseases.

Further particulars from: Dr M. Donald Blaufox, Department of Nuclear Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.

54th Congress of the Belgian Society of Urology

Brussels, Belgium. 27–28 May 1989

The topic will be "Lower Urinary and Genital Pathology in Children."

Further particulars from: Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.

XVIIIth Annual Conference of the European Dialysis and Transplant Nurses Association—European Renal Care Association

Göteborg, Sweden. 11–14 June 1989

XXVIth Congress of the European Dialysis and Transplant Association—European Renal Association

Göteborg, Sweden. 11–15 June 1989

Further information from: General and Scientific Secretariat, Transplant Unit, Department of Surgery, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

Canadian Urological Association

Quebec City, Canada. 18–22 June 1989

Further information from: Dr J. P. Collins, B–3, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.

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REVIEW

Wilms' Tumour and Genitourinary Rhabdomyosarcoma

D. C. S. GOUGH

Department of Paediatric Urology, Royal Manchester Children's Hospital, Manchester

The first successful nephrectomy for nephroblastoma was by Jessop in 1877. Radiotherapy was introduced by Friedlander (1916) and an effective chemotherapeutic agent in the form of actinomycin (Farber *et al.*, 1956) led to rapid advances in drug treatment which were accelerated by the introduction of vincristine (Sutow *et al.*, 1963).

Despite the availability of therapy, the results of treatment were patchy, with little more than one-third of patients surviving during the 1960s in England (Ledlie *et al.*, 1970).

The most significant advance in the last 20 years has not been the availability of new agents but the centralisation of care, which has developed individual clinical expertise and given all patients the chance of the very best available therapy (Kramer *et al.*, 1984).

Three major collaborative groups came into being after 1969—the National Wilms' Tumor Study Group (NWTS) in the United States, the International Society of Paediatric Oncology (SIOP) in Europe, and the United Kingdom Children's Cancer Study Group (UKCCSG). These three groups have had a major influence on treatment and survival, with more than 90% of all British patients being referred to the UKCCSG for management, and the 3-year survival rate of Wilms' tumour patients in this country now exceeds 80%.

These survival figures have, however, been attainable for more than a decade and it is the refinement of treatment protocols, with reduction in treatment-related toxicity, that has been the major contribution in this recent period.

Accepted for publication 9 March 1988

Tumour Staging

Factors such as age, sex and tumour weight are no longer recognised as providing any prognostic value. Treatment is now based on clinicopathological staging and the presence or absence of unfavourable histological (UH) features; 1 child in 10 has a tumour with anaplastic or sarcomatous elements, associated with a higher clinical stage, greater risk of recurrence and poor response to treatment.

The current staging system is as follows:

Stage I

Localised disease inside the renal capsule with complete surgical removal.

Stage II

Penetration of the renal capsule with tumour but complete surgical excision. "Local" rupture during removal.

Stage III

(1) Pre-operative tumour rupture.
(2) Surgical spill involving the whole peritoneal cavity during removal.
(3) Lymph node metastases in surgical specimen.
(4) Tumour inoperable at initial laparotomy.

Stage IV

Metastases present at diagnosis, *e.g.* lung, liver or bone. (Lung metastases not visible on chest X-ray but positive on computed tomography scans do not make the patient stage IV).

Stage V

Bilateral disease at initial diagnosis. A needle biopsy does not affect the clinical stage of the disease, other than making a stage I case into stage II.

The Role of Surgery

Without any other form of treatment, surgery alone will cure a maximum of 25% of patients, but recurrent disease in the abdomen or lungs will ultimately appear in the remainder. It would appear from historical data that resection of the primary tumour may be essential to survival in stage I to IV (Ledlie *et al.*, 1970), since there were no survivors amongst those patients not having a radical nephrectomy.

Surgical mortality is now 1 to 2% in the current UK study, which compares favourably with mortalities of 1 to 5% in previous series. Intra-operative mortality is usually due to tumour embolus, and careful pre-operative assessment of the patient helps to reduce this risk.

The renal vein and inferior vena cava are involved in 6% of patients and half show no clinical signs that suggest vascular invasion (Clayman *et al.*, 1982). Dilated veins in the lower half of the body or signs of raised central venous pressure due to intracardiac extension of tumour thrombus are exceptionally rare. Hypertension, albuminuria or signs of hepatic dysfunction are associated with venous involvement and should always lead to further pre-operative investigation.

Angiography of the vena cava by direct femoral puncture is safe, with no reported cases of tumour embolism. Ultrasound has also proved reliable, but studies suggesting caval occlusion may be caused purely by the weight of tumour pressing on the vessel; under such circumstances, reappraisal in the lateral or prone position may clarify the true diagnosis (De Campo, 1986).

Computed tomography has been less helpful, as blood and tumour thrombus have the same attenuation (Steele *et al.*, 1978); despite the use of all three studies, 30% of major vascular involvement can be missed, with this figure rising when non-invasive imaging is relied upon (Nakayama *et al.*, 1986).

The surgical approach to patients with vascular invasion should be cautious, since more than half of the deaths in Wilms' tumour surgery are related to tumour embolism during operation, which causes sudden cardiorespiratory collapse in the absence of major haemorrhage. Emergency pulmonary embolectomy is the patient's only hope of survival under these circumstances, with several such cases having been reported with a long-term successful outcome.

The surgery of caval tumour may be complicated further by the fact that simple proximal and distal control with cavotomy and embolectomy may be impossible owing to tumour adherence to the vessel wall. To gain complete surgical clearance, partial resection of the vena cava with venous bypass of the remaining kidney may be necessary. Major tumour embolism seldom occurs before surgery and where such involvement is found pre-operatively, the commonest clinical approach in the United Kingdom is to treat the patient with chemotherapy initially and to re-assess the level of vascular involvement some weeks later, depending upon the degree of clinical response. The degree of tumour shrinkage which can occur on this regimen is such that vascular involvement is no longer a problem and straightforward radical nephrectomy is possible (Kogan *et al.*, 1986).

Intra-cardiac tumour may demand a completely different surgical approach, with cardiopulmonary bypass allowing direct access to the right atrium for tumour removal, as well as the extension into the upper part of the cava and hepatic veins.

Every effort should be made to clarify the extent of tumour before operative intervention, and an inferior venacavogram and ultrasound assessment should be performed in every patient. If a decision is made to attempt removal of a major tumour thrombus, the immediate availability of a cardiovascular surgeon should be assured.

Where pre-operative assessment has led to a planned approach along these lines, the morbidity and mortality rates can be dramatically reduced, with the current NWTS study showing 86% survival in this situation (Nakayama *et al.*, 1986).

Because of duodenal, caval or aortic involvement, the tumour is found inoperable in 10% of patients where surgery is the primary therapy, and recent analysis of this group has indicated a worse prognosis, with only 50% of patients surviving in the long term. Pre-operative CT scanning may help the surgeon to make a decision about initial laparotomy and nephrectomy and there is no doubt that pre-operative treatment with vincristine can cause tumour shrinkage and reduce the incidence of intra-operative complications such as tumour rupture (Table 1).

Historical data from SIOP indicated that recurrence-free survival was greater in those patients in whom the tumour did not rupture during resection, although the overall survival rate was not adversely

Table 1 Intra-operative Tumour Rupture Rate

SIOP 1	32% with primary tumour resection
NWTS 1	16% with primary tumour resection
SIOP 1	4% with pre-op radiotherapy
SIOP 2	5% with pre-op chemotherapy

affected. Their studies then concentrated on pre-operative therapy, which now consists of a short course of vincristine.

Figures from the SIOP study suggest that primary inoperability is very rare where pre-treatment has occurred. Those who argue against the primary treatment of Wilms' tumour patients with chemotherapy point out that 3% of patients are initially misdiagnosed and at nephrectomy are shown to have a benign lesion (Ehrlich, 1983).

The overall success rate of treatment in SIOP, NWTS and UK studies are comparable, and protocols in the United Kingdom do allow for pre-treatment where the clinician regards this as advisable. Percutaneous biopsy to confirm the nature of the tumour before treatment does not appear to be hazardous or to affect the ultimate outcome. Most patients, however, will still have a primary nephrectomy, and where necrotic tissue is entered during the dissection or where the tumour ruptures, care should be taken to limit the spill to the flank. Should the tumour rupture and disseminate through the peritoneal cavity, post-operative radiotherapy is advisable and the patient should be treated as stage III disease.

The lymph node status of the patient is vital information for staging and treatment and some form of lymphadenectomy should be practised at the time of extirpative surgery, but there is no evidence that radical abdominal lymphadenectomy confers any benefit.

Careful examination of the contralateral kidney as part of an exploratory laparotomy is accepted by all, but few in fact fully mobilise the contralateral kidney to inspect its posterior surface; only 30% of those participating in the MRC and UKCCSG trials do so. Those who make this a routine practice are, of course, the only practitioners who find tumours on the posterior surface of the kidney at initial nephrectomy. Since the commonest site of abdominal "recurrence" in stage I and II disease is the remaining kidney, knowledge of these factors may encourage more surgeons to inspect routinely its posterior surface at initial operation, as it is possible that patients relapsing in this way were initially stage V at presentation.

Some 5% of patients have bilateral disease at presentation and survival in this group is generally excellent (Bishop *et al.*, 1977). The treatment producing these good results has been nephrectomy of the major lesion and, where anatomically possible, partial nephrectomy of the smaller tumour.

Pre-operative chemotherapy may make this decision easier and allow greater confidence in surgical tumour clearance. It is difficult to assess whether complete surgical clearance should be attempted in stage V patients, as in the first NWTS study 19 of 22 patients with apparent residual disease in remaining renal tissue were alive 2 years later. A more recent study found that despite chemotherapy and radiotherapy, cure cannot be guaranteed when residual renal tumour remains, with 25% of patients relapsing at this site (Cohen *et al.*, 1986).

Nearly one-third of bilateral cases are diagnosed clinically pre-operatively and here bilateral biopsy is suggested to confirm the diagnosis. Treatment with chemotherapy (and radiotherapy if poorly responding) should allow re-assessment after approximately 2 months of treatment. Exploratory surgery should aim for tumour clearance at this time and angiography helps in this assessment.

A further one-third of patients with stage V disease are not suspected as such clinically but are shown to have a second tumour on intravenous urography. Angiography should allow a planned surgical approach with partial nephrectomy of the smaller tumour.

The remaining third of patients in stage V are found at laparotomy, having been unsuspected on all pre-operative studies. Following nephrectomy of the major lesion, a safe approach in this group would seem to be biopsy alone, with chemotherapy appropriate to the stage of the contralateral tumour, and abdominal radiotherapy.

Most survivors in stage V disease have also had abdominal radiotherapy (Bishop *et al.*, 1977; Cohen *et al.*, 1986). Current figures from the United Kingdom show that disease-free survival with this approach in stage V disease is 70%.

Mesoblastic Nephroma

These tumours are usually found in the neonatal period and where the diagnosis is certain, no further treatment is necessary. Before histological confirmation is obtained they are often confused clinically with Wilms' tumour, presenting with a mass lesion in the kidney.

They should be regarded as benign tumours with malignant potential and only those presenting outside the neonatal period need to be followed up closely after excision (Shanbhogue *et al.*, 1986).

None of the 10 mesoblastic nephromas followed in the current UKCCSG study has displayed any malignant potential.

Radiotherapy

Survival from Wilms' tumour was still considered poor until the advent of radiotherapy. Combinations of surgery and post-operative irradiation of the tumour bed resulted in 50% long-term survival (Gross and Neuhauser, 1950). This survival was often achieved at the expense of spinal column shortening or scoliosis if only one-half of the spine had been irradiated. Less often, toxicity to the liver or gonads would be manifest in the long term, as would necrosis of the femoral head.

Just as the quality of surgery has improved, so has radiotherapy. Clinical trials, particularly those conducted by NWTS, have shown that with favourable histology, major reductions in radiotherapy dosage were possible down to 1000 cGy, and in many instances radiotherapy can be replaced by chemotherapy. It is now used where residual disease is likely to be present (such as stage III cases) and in all of those where a high risk of recurrence is known—unfavourable histology patients. It would also seem valuable therapy in stage IV cases, where pulmonary irradiation in conjunction with chemotherapy offers better survival than with either therapy alone. The risks of radiation pulmonary fibrosis and almost certain death can be averted by keeping the pulmonary dosage below 1200 cGy (Tefft, 1977).

The current UKCCSG study has also tried to avoid post-operative radiotherapy to those patients with unfavourable histology, relying on the proven presence of intra-abdominal disease some 16 weeks from diagnosis to determine whether radiotherapy is to be given. This was to be confirmed by "second-look" laparotomy and only patients with proven evidence of intra-abdominal disease would receive radiotherapy, accepting its permanent effects on bone growth. However, current chemotherapy seems to have been so effective that very little evidence of residual disease has been found at this time and it may be possible to drop both radiotherapy and second-look laparotomy from the protocol.

Chemotherapy

Despite the success of surgery and radiotherapy in saving half of the patients with Wilms' tumour, metastatic disease, usually in the lungs, caused death in the remainder.

It is chemotherapy that controls this metastatic disease and the three most commonly used drugs are vincristine, actinomycin D and Adriamycin. Proof that this is indeed the case comes from current studies in stage I to III patients who are chest X-ray negative and CT positive for lung metastases at diagnosis. Chemotherapy causes resolution of such metastases without evidence thus far of pulmonary relapse (Gough, unpublished data). Treatment morbidity is not inconsiderable and includes the following:

Clinically significant myelosuppression: 22%
Weight loss (> 10%): 18%
Vincristine neurotoxicity: 10%
Gastro-intestinal toxicity: 10%
Hepatic toxicity: 5%

During chemotherapy some 2% of patients die of treatment toxicity.

Considerable clinical judgement is required during the treatment as many agents potentiate one another. Hepatic toxicity, for instance, is accentuated by hepatic venous occlusion, hepatitis and multiple general anaesthesia, and can be potentiated by radiotherapy and high dose actinomycin therapy. It can present as a combination of jaundice and ascites, or merely thrombocytopenia. Subsequent therapy needs to be carefully reduced and tailored directly to patient needs when any toxic effects are observed.

Long-term chemotherapy is most often delivered through indwelling Hickman central venous catheters, which allow repeated blood sampling and easy access for chemotherapy without repeated needling.

Relapse of Disease

The pattern of relapse is illustrated in Table 2, with pulmonary metastases being the most frequent, often in combination with relapse elsewhere.

Abdominal relapse alone is rare and most commonly occurs as late relapse in the remaining

Table 2 Pattern of Recurrent disease (Lemerle *et al*, 1983)

Number of patients in trial	164
Relapse in lung only	22
Relapse in lung and abdomen	13
Relapse in abdomen alone	4
Relapse in liver alone	2
Relapse in bone alone	1

kidney in previous stage I disease. When metastases occur in bone there is no recorded survival. Our own experience with surgical treatment of relapse has not been good, but the general principle of combination chemotherapy, radiotherapy and surgical resection of clearly localised disease in lung or liver has been accepted. The chances of successful treatment are related to initial staging and the current figure in the UK suggests that relapse is treatable in 70% of stage I patients, 50% of stage II, and only 10% of stage III and IV patients (Gough, unpublished data).

Isolated metastases which are likely to respond to surgery are now unusual and current relapse therapy depends to some extent on previous treatment. If the patient has already received vincristine and actinomycin D, then Adriamicin, ifosfamide and etoposide are drugs known to be effective in inducing a remission and cure of disease. Radiation therapy to relapse sites would also be given.

Late relapse of disease can and does occur in Wilms' tumour patients. The usual criteria for cure would be disease-free survival at 3 years, but relapse after 5 years has been noted in 3 cases followed on the Manchester Tumour Registry. All of these patients have died of distant metastases and were found amongst 90 long-term survivors (Birch *et al.*, 1987).

Surveillance of High Risk Groups

Several clinical groups can be identified where the development of nephroblastoma is relatively commonplace and where regular surveillance is advised. The frequency of investigation and the mode of evaluation is usually by ultrasound study every 4 months for the first 5 to 8 years of life and 6-monthly thereafter during childhood. This approach has been successful in the early diagnosis and treatment of one particular high risk group (Friedman, 1986).

In addition to sporadic aniridia, the other conditions subject to surveillance are Beckwith syndrome (exomphalos, macroglossia and gigantism), Drash syndrome, (pseudohermaphroditism, glomerulopathy and Wilms' tumour), Perlman syndrome (familial renal dysplasia, multiple congenital abnormalities) and patients with hemihypertrophy.

The Future

Investigative groups have arrived at a point in treatment where it seems difficult to make further progress and treatment schedules are reduced to what most would accept as the minimum. The relative role of each treatment modality seems relatively well defined and no major breakthroughs in therapy are likely to occur without new agents.

It has been suggested that more conservative surgery may be adopted in the future (Kelalis, 1986) but this approach seems to have little to commend it, except perhaps in stage I disease, where relapse in the contralateral kidney has been most common. One of the difficulties encountered with such a relapse is the ability to preserve sufficient functioning renal tissue. Only once has this occurred in my own hospital and temporary peritoneal dialysis was required following partial nephrectomy with long-term survival. In larger groups of patients with bilateral tumours, renal failure is not an unusual cause of death (Cohen *et al.*, 1986). Conservative surgery in stage II, III and IV disease seems to have little theoretical benefit and does not make surgery any simpler.

Results of Treatment

Survival in the United Kingdom is excellent for patients treated within the UKCCSG; the results in Table 3 are from the current UK study at the end of 1986 and are based on the treatment outlined in Table 4.

Table 3 Wilms' Tumour: 3-year Survival Rates

	Stage	%
Favourable histology (n = 238)	I	95
	II	95
	III	82
	IV	59
	V	67
Unfavourable histology (n = 33)	All stages	61

Table 4 Summary of Therapy

Favourable histology	
Stage I	Surgery + vincristine for 3 months
Stage II	Surgery + vincristine and actinomycin D for 6 months
Stage III	Surgery + 2000 cGy + vincristine, actinomycin D + Adriamicin for 1 year
Stage IV	Triple chemotherapy + surgery + abdominal and pulmonary irradiation, then chemotherapy for 1 year
Unfavourable histology	
Stage I and II	Surgery + 3 drugs for 6 months
Stage III and IV	Surgery + 3 drugs for 1 year (± radiation therapy)
Stage V	See text

Poor survival figures in stage IV cases were noted in the UK study when comparison was made with the results reported by other investigators, and pulmonary irradiation is now routine for stage IV cases.

Genitourinary Rhabdomyosarcoma

Despite the statement that rhabdomyosarcoma is the commonest soft tissue sarcoma in childhood, it remains a very rare tumour. With an annual incidence of 50 cases, this means a total of some 17 genitourinary cases each year in the United Kingdom, as one-third of cases originate in these sites:

1. Bladder and prostate tumours which present with symptoms of dysuria, retention and usually a palpable lower abdominal mass.
2. Vagina and cervix lesions in the female, presenting with a blood-stained vaginal discharge or the presence of watery globular tumour obvious at the vaginal orifice.
3. Paratesticular tumours which appear as a painless rapidly growing tumour in the scrotum or spermatic cord.

Few of us will ever develop a major clinical experience with this tumour and the basis of our current knowledge comes from historical data and the current Intergroup Rhabdomyosarcoma Study (IRS), based in the United States, which receives patient data from centres throughout the world and has co-ordinated trials since 1972.

Not only is the tumour infrequently encountered but it was also infrequently cured, with few individuals showing any benefit from treatment before 1960 and survival only about 20% in 1970 (Birch *et al.*, 1987).

Treatment depends not only on the site of origin but on the current IRS grouping which is outlined in Table 5.

Table 5 IRS Grouping

Group I disease
Localised tumour with complete surgical resection

Group II disease
(Residual microscopic tumour)
(a) Tumour margin microscopically invaded
(b) Major regional disease but totally resected histologically
(most distal lymph node clear of disease)
(c) Lymph node positive disease
(most distal lymph node in specimen involved)

Group III disease
Incomplete resection or biopsy only

Group IV disease
Metastasis at diagnosis

Bladder and prostate lesions

Radical surgical resection combined with chemotherapy in the first IRS study showed that 90% of children were alive, free of disease, but with urinary diversion 3 years later. A more conservative approach of initial chemotherapy and limited resectional surgery was then adopted for the second IRS study reported by Hays *et al.* (1982). This caused some concern when 27% of patients died of disease and only 38% had bladder salvage; a number of these required further bladder surgery with augmentation or diversion because of the complications of radiation cystitis

Following the criticism of poor tumour control with chemotherapy, the treatment was intensified in the third study and consisted of vincristine, Adriamicin and cyclophosphamide (VAC) plus cisplatin and dactinomicin, and this intensive chemotherapy approach has also been adopted by SIOP workers. On this regime patients should develop a rapid clinical response if the therapy is likely to be effective. Regular assessment of response is important as attempts at surgical salvage late in the course of this disease are usually unsuccessful (Fleming *et al.*, 1984).

Where clinical response is partial, radiotherapy will increase tumour resolution when given in doses of 5000 cGy to bulk disease, with 6/6 patients showing long-term survival without any resectional surgery in one study (Kaplan *et al.*, 1983). The excellent results from this study have not been universally achieved and in general there is a failure of medical and radiotherapy treatment, with major surgical resection being necessary in 40% of patients (Ghavimi *et al.*, 1984), and this would be more in keeping with the general experience in this tumour site.

Rhabdomyosarcoma of the vagina and cervix

The results at this site seem particularly good, with all patients without metastases surviving even when complete surgical removal was not undertaken (Hays *et al.*, 1981). As in all cases of genitourinary rhabdomyosarcoma where metastasis had occurred before diagnosis, survival was not obtained in any case, with lesions of the cervix more likely to have spread to lungs or marrow at the time of initial diagnosis.

Tumour control with chemotherapy followed by local surgical excision and radiotherapy for macroscopic incomplete removal seems to offer an excellent long-term result.

Paratesticular Tumours

The basic surgical treatment for this condition is radical orchiectomy and the results of treatment in Group I disease are excellent; the use of radiotherapy is unnecessary as chemotherapy (VAC) leads to cure in nearly all cases. Survival in Group II cases is probably increased by the use of radiotherapy (4000 cGy) to regional lymph nodes (Grosfeld *et al.*, 1983) but in the few reported cases drops to about 50% (Fleming *et al.*, 1984). Those patients known to have distant metastasis at the time of diagnosis have no recorded survival.

The main area of debate with this particular disease concerns the value of staging laparotomy with retroperitoneal lymphadenectomy. There seems no evidence to suggest that this is in any way therapeutic and when the patients have been staged with lymphangiography and CT scans, excellent results have been obtained without staging laparotomy (Quesada *et al.*, 1986).

The Future

The place and timing of surgical excision in major pelvic tumours is not yet fully established, particularly with regard to bladder and prostatic lesions. Some of the recent reports have done little to clarify the issue but there is no doubt that with extensive local surgery, adjunctive chemotherapy and radiotherapy a complete cure is to be expected in patients not showing distant metastasis at diagnosis.

It is equally clear that in approximately one-third of cases cure can be expected without any surgical intervention, but delay in tumour excision can lead to a loss of local control, metastasis and death.

The present approach in the IRS III study is that by 16 to 20 weeks from diagnosis some attempt at assessment of residual tumour bulk and site is obtained by computed tomography scanning, examination under anaesthesia and biopsy. This should then lead to a decision with regard to further therapy. Radiation treatment follows when microscopic residual disease is diagnosed in Stage II or III cases and should lead to an excellent prognosis. The role of surgery is to control non-responsive disease at any stage in this assessment process. The uncertainty which remains is the relative value of radiation and surgical treatment at the 16 to 20 week stage. Perhaps surgical excision should be substituted at 16 weeks, obtaining clearance of residual tumour. This will only become clear as trials proceed.

In those with distant spread, current studies offer more and more intensive medical treatment, sometimes with autologous bone marrow transplantation.

Five-year survival from all forms of rhabdomyosarcoma in our institution is 54% (Birch *et al.*, 1987) and the current prognosis depends on histological type and the degree of spread at diagnosis.

Alveolar, anaplastic or monomorphous tumours account for 20% of the overall incidence and reduce the 3-year survival rate from 78 to 47%.

Mixed type (favourable histology) is found most frequently in genitourinary tumours and is partly responsible for their relatively good prognosis.

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Urological History-taking and Management Recommendations by Microcomputer

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Summary—A system has been developed to acquire a complete urological history using an Apple microcomputer. The system can ask up to 300 multiple choice questions which the patient answers using a light pen. The questions are grouped into blocks for urological symptoms and complicating factors. A printout summarises the history and the recommended further investigations. A copy of this is given to the patient and the referring doctor. The clinician discusses the printout and proposed investigations with the patient. The system has been tested against experienced clinicians and the results are presented. The computer system was evaluated for 26 patients and was found to record all of the important information. The system is now in regular use in the out-patient clinic as the first part of the diagnostic work-up in suitable referrals. This system has shortened waiting times for first appointments. To date 261 patients have used the system. The consultant urologist continues his practice of reading all referral letters and allocating priorities. Conditions requiring immediate physical examination (*e.g.* testicular swelling) are not suitable for this type of approach.

Urology is ideally suited to computerised history-taking and management recommendation because there are eminently logical and clear paths to follow in urological investigation (Glen, 1983, 1987). Gastrointestinal clinics in this hospital and elsewhere have demonstrated high patient compliance when using computer interrogation systems (Lucas *et al.*, 1976; Knill-Jones *et al.*, 1985). Local general practitioners have been enthusiastic in their support of this approach and there is also wider support (Pringle, 1988). The heavy urological workload stimulated this department to design a computer system to perform the bulk of the work involved in the first consultation by acquiring and printing the presenting clinical history along with recommendations for initial investigations. The original printout goes into the hospital notes and copies are printed for the patient and the referring practitioner. The patient leaves the department with appointments for the necessary further investigations and two copies of the printout. The patient is asked to deliver one copy of the printout to the GP, retaining the other for alteration or addition if appropriate.

We report the design of this system and the results of the pilot study, comparing histories and investigations generated by the computer system with those of clinicians conducting an out-patient clinic. Now in routine use, this system enables up to 14 additional new patients to be investigated each week.

Patients and Methods

Computer system

The programs for computer interrogation were developed jointly by our senior grade physicist, a university computing student on attachment and the urologists. At present the programs are implemented in BASIC on an Apple II computer with 48k memory, since this was the only equipment available.

In taking a clinical history a clinician modifies the flow of questions in the light of answers obtained, accelerating the acquisition of relevant information. To simulate this process, the initial

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Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988 stage in the development of software was the production of an extensive list of all possible questions which a urologist might ask and a set of conditions under which each question is asked. The programmers then translated this expert knowledge into a flow chart which defines the path through the questions. The flow chart was encoded into an 8 × 300 array; 300 is the current maximum number of questions and 8 is the maximum number of possible responses to any question. All of the questions are in the multiple choice format. The program accesses this array using as indices the question it has just asked and the response of the patient. The element stored in the array at that location is the number of the next question.

Adaptability is important to allow development and we have written support software which enables ready modification of any part of the interrogation process by easy to run programs. Examples of developments which can be performed by the support software are:

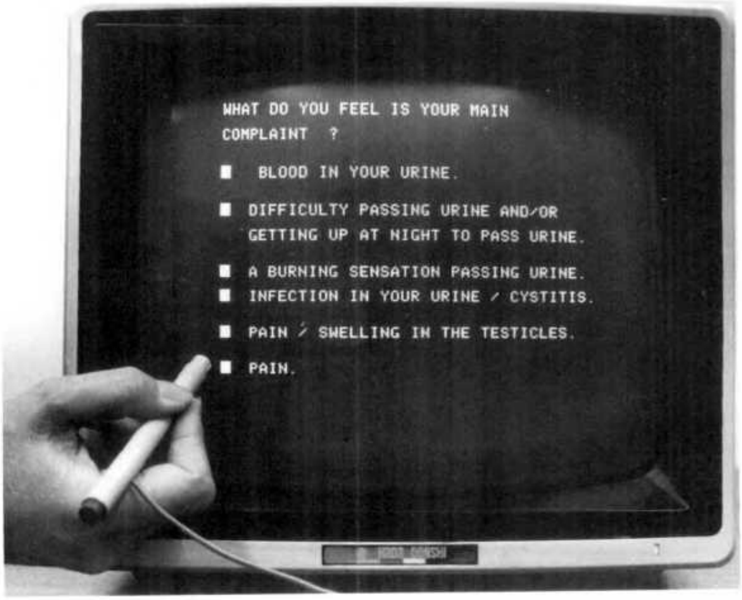
1. Change of the wording of a question.
2. Insertion of an alternative explanation of a question which the patient can trigger via a "Don't Understand" option on the screen.
3. Alteration of the logical flow of the interrogation.
4. Addition of new questions.

History-taking

The patient sits before the computer monitor screen and is presented with a question below which are a number of possible responses. The patient uses a light pen to indicate the most appropriate response (Fig. 1).

The program first gives a list of possible main symptoms in patient friendly language, covering haematuria, bladder outlet obstruction, infection, pain, testicular swelling and incontinence. The blocks and certain questions within the blocks are modified by sex and age of patient. For example, women over a certain age are not asked whether they may be pregnant. Once the patient has indicated which of these problems are present a block of questions is asked, obtaining a full history for each symptom. It is possible for the patient to indicate symptoms from more than one block. After the urological history a group of questions on basic general health is asked, including questions relating to fitness for subsequent investigations. The patient can enter as many blocks as are required to elicit the full urological and basic general history (Fig. 2).

The system prints out a summary of the patient's history under the headings of the main symptoms along with recommendations for further investigations. A recommendation may be qualified if the patient's history has uncovered a contraindication. For example, intravenous urography may be indicated, but if any allergy is recorded the system will generate a warning on the printout. Similarly, if the patient is unfit for anaesthesia as a day-patient owing to cardiovascular disease or other factors,



WHAT DO YOU FEEL IS YOUR MAIN
COMPLAINT ?

■ BLOOD IN YOUR URINE.

■ DIFFICULTY PASSING URINE AND/OR
GETTING UP AT NIGHT TO PASS URINE.

■ A BURNING SENSATION PASSING URINE.
■ INFECTION IN YOUR URINE / CYSTITIS.

■ PAIN / SWELLING IN THE TESTICLES.

■ PAIN.

Fig. 1 A patient using the light pen. The programs differentiate between sexes: this is the male screen.

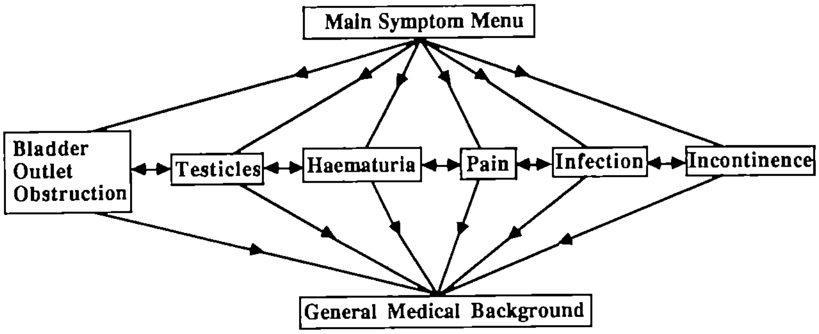


Fig. 2 The question blocks available to the program.

this is highlighted. An example of a printout generating such qualifications is shown in Figure 3.

Patient compliance

Studies carried out in the Gastrointestinal Department of this hospital showed a high level of acceptability for computer interrogation (Lucas *et al.*, 1976). We have used equipment similar to that used in these studies and a similar multiple choice format for our questions. Only one patient refused to finish the urological interrogation, being late for an appointment elsewhere. The only consistent complaint is that the time lapse between each group of questions is excessive—a problem that will be overcome with a faster computer. At present, interviews take from 20 to 30 min. However, most patients are happy to have ample time.

Results

The system's performance with the first 26 patients was judged under the following headings:

1. Recording of symptoms.
2. Recommendations for investigations.
3. Recording of important complicating factors including allergies, asthma, cardiovascular disease and other medical conditions which would complicate management.

The computer system's findings were compared with those of the clinician who saw the patient earlier the same day in the out-patient clinic.

A clear requirement of the computer system was that it should record everything that the clinician had recorded. This was confirmed. Of the 41 urological symptoms and 11 complicating factors noted by the clinicians, all were also recorded by the computer system. In addition, in 23 of the 26 patients the system picked up symptoms or complicating factors which had not been elicited by the clinician. This information is summarised in the Table. In some patients more than one additional item of information was recorded by the system.

The clinician recommended cystourethroscopy in 23 patients and intravenous urography (IVU) in 21. The computer system recommended all of these, but in addition recommended 1 further patient to have both IVU and cystourethroscopy and 3 further patients to have IVU only. The clinician recommended 11 patients to have urodynamic studies, all of which were also recommended by the computer system. The system produced no unnecessary urodynamic recommendations.

The clinician vets the printout and authorises appropriate investigations.

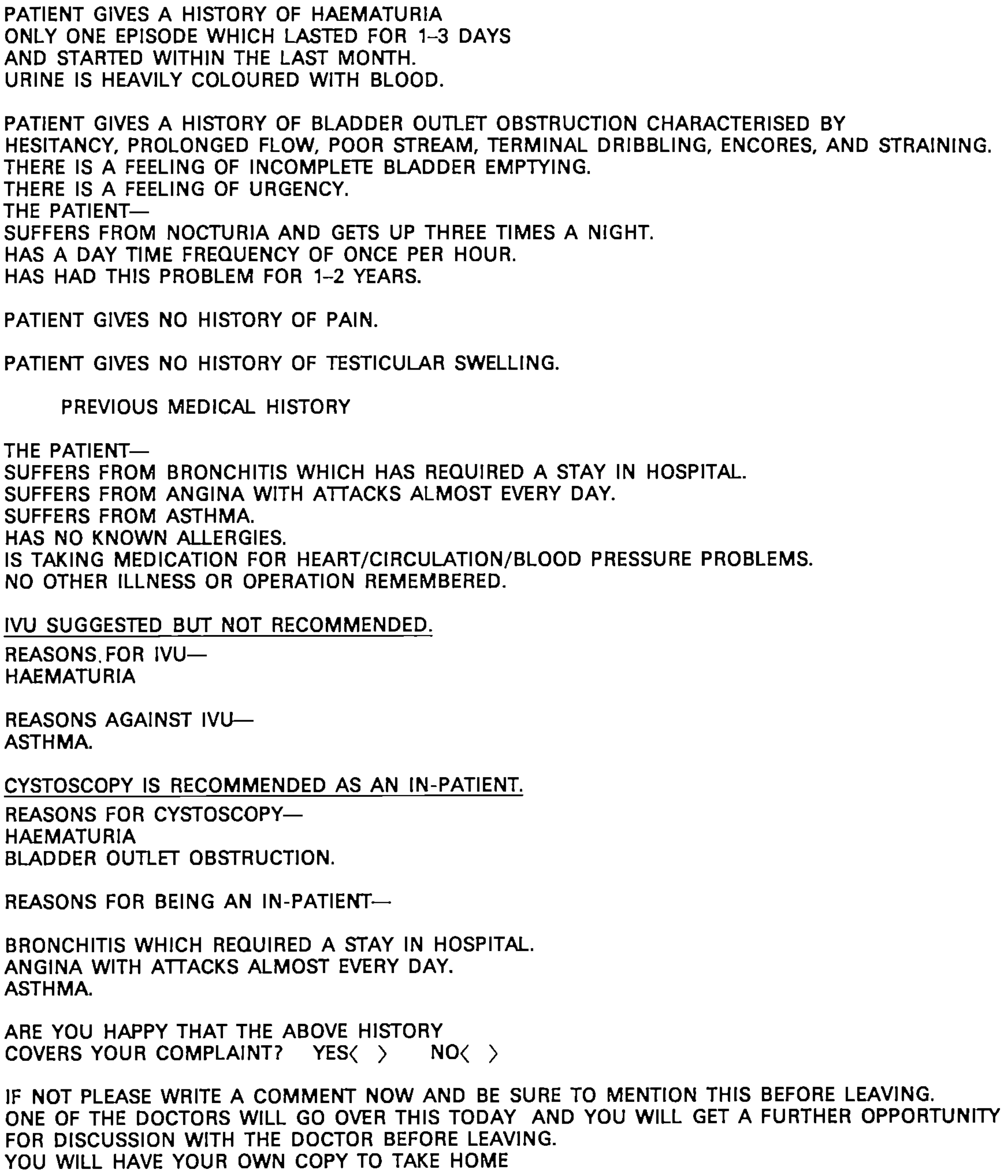
Discussion

The computer system is sensitive, taking a very detailed urological history. No major symptoms or complicating factors have been missed in the 26

Table Extra Information Detected by Computer and Missed by Clinician (not all affecting management)

Symptom	*No. of patients*
Pain	10
Infection	10
Bladder outlet obstruction	3
Subjective testicular swelling*	3
Incontinence	2
Complicating factors	
Epilepsy	1
Asthma	1
Steroid therapy	1
Previous anaesthetic problem	1
Bronchitis	1

* Testicular swelling reported by patient, not confirmed by clinician on examination



```
PATIENT GIVES A HISTORY OF HAEMATURIA
ONLY ONE EPISODE WHICH LASTED FOR 1-3 DAYS
AND STARTED WITHIN THE LAST MONTH.
URINE IS HEAVILY COLOURED WITH BLOOD.

PATIENT GIVES A HISTORY OF BLADDER OUTLET OBSTRUCTION CHARACTERISED BY
HESITANCY, PROLONGED FLOW, POOR STREAM, TERMINAL DRIBBLING, ENCORES, AND STRAINING.
THERE IS A FEELING OF INCOMPLETE BLADDER EMPTYING.
THERE IS A FEELING OF URGENCY.
THE PATIENT—
SUFFERS FROM NOCTURIA AND GETS UP THREE TIMES A NIGHT.
HAS A DAY TIME FREQUENCY OF ONCE PER HOUR.
HAS HAD THIS PROBLEM FOR 1-2 YEARS.

PATIENT GIVES NO HISTORY OF PAIN.

PATIENT GIVES NO HISTORY OF TESTICULAR SWELLING.

     PREVIOUS MEDICAL HISTORY

THE PATIENT—
SUFFERS FROM BRONCHITIS WHICH HAS REQUIRED A STAY IN HOSPITAL.
SUFFERS FROM ANGINA WITH ATTACKS ALMOST EVERY DAY.
SUFFERS FROM ASTHMA.
HAS NO KNOWN ALLERGIES.
IS TAKING MEDICATION FOR HEART/CIRCULATION/BLOOD PRESSURE PROBLEMS.
NO OTHER ILLNESS OR OPERATION REMEMBERED.

IVU SUGGESTED BUT NOT RECOMMENDED.
REASONS.FOR IVU—
HAEMATURIA

REASONS AGAINST IVU—
ASTHMA.

CYSTOSCOPY IS RECOMMENDED AS AN IN-PATIENT.
REASONS FOR CYSTOSCOPY—
HAEMATURIA
BLADDER OUTLET OBSTRUCTION.

REASONS FOR BEING AN IN-PATIENT—

BRONCHITIS WHICH REQUIRED A STAY IN HOSPITAL.
ANGINA WITH ATTACKS ALMOST EVERY DAY.
ASTHMA.

ARE YOU HAPPY THAT THE ABOVE HISTORY
COVERS YOUR COMPLAINT?   YES( )    NO( )

IF NOT PLEASE WRITE A COMMENT NOW AND BE SURE TO MENTION THIS BEFORE LEAVING.
ONE OF THE DOCTORS WILL GO OVER THIS TODAY AND YOU WILL GET A FURTHER OPPORTUNITY
FOR DISCUSSION WITH THE DOCTOR BEFORE LEAVING.
YOU WILL HAVE YOUR OWN COPY TO TAKE HOME
```

Fig. 3 Sample printout showing history and recommendations. Identification data are omitted

patients. In fact the system has proved to be consistently more detailed than the experienced clinicians in our department. This has had a significant bearing on patient management, for example where epilepsy or asthma has been uncovered. One other occasions the system was more sensitive in recording conditions such as urinary infection, which will be part of the history of many women. The clinician may not see it as of prime importance at the first clinical interview and may be more interested in a recent episode of acute pain. The system was very good at recording complicating medical conditions. Eleven such conditions were recorded; 6 of these, severe hypertension, angina, myocardial infarction, asthma, bronchitis and diabetes, were also picked up by the clinician and 5 were not. The 5 are listed in the Table.

The system's proposals for investigation were thought unnecessary by the clinician in 4 cases. In 1 of these the patient presented with a history of bladder outlet obstruction which was prostatic in origin. One of the patient's symptoms was urinary frequency, which led the computer system into the block of questions on infection and subsequently to recommending an unnecessary IVU. In 3 of the 4 cases the patient complained of pain which the clinician did not feel was of urological origin. Thus the investigations recommended by the computer were not necessarily appropriate. This reflects a lack of subtlety in the computer system when eliciting a history of pain. At present our system can ask a maximum of 300 questions, owing to limited memory with the Apple II. We are planning further development of the system on a more versatile computer, at which stage the pain and infection histories will be made more precise. In contrast, the urodynamic recommendations of the computer system correlated exactly with the clinician's, demonstrating that the questions asked about continence were adequate. These results emphasise the need for an experienced clinician to see the printout at the time and authorise or block the recommended investigations. This task is much less time-consuming than a conventional consultation.

Computerised urological history-taking and management recommendation has been successful in this department and is now in routine use for suitable new patients. An experienced clinician sees every printout before the patient leaves the department. The clinician is free to be involved in other duties while the computer history is being taken. This leads to a more efficient use of a clinician's time and has already reduced the waiting time for a first clinic appointment. Patients have ample opportunity to correct or add to the printout, both in the department or at home. The secretaries welcome the reduction in their workload at the new clinic.

The system has been written with development in mind. The support software enables the system to be easily modified as experience increases.

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Intrarenal Duplication

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Summary—We report the anomaly of intrarenal duplication seen during the course of investigation of urinary tract infection in 6 children. The anomaly and its embryological basis are described.

The term "intrarenal duplication" is used here to describe a variant of bifid pelvis where the superior calix drains the upper half of the kidney through a long narrow pelvis into the middle calix or lower pelvis with a single extrarenal ureter.

Patients and Methods

The anomaly was seen in 6 children during the course of investigation of urinary tract infection. It was present in the left kidney in 3 patients; the other 3 had a horseshoe kidney and showed intrarenal duplication of the right moiety in 2 and of both sides in the third.

The abnormality was seen on IVU in all patients (Fig. 1) and on retrograde pyelography in 1 (Fig. 2); a ^{99m}Tc DMSA isotope scan showed demarcation between the upper and lower halves of the kidney, suggesting renal duplication (Fig. 3). The kidney with intrarenal duplication was longer than its contralateral kidney as measured on IVU and/or sonar examination.

Discussion

The extent of the kidney duplication depends upon the extent to which the two ureteric premordia diverge from one another before reaching the nephrogenic blastema. The duplication may be indicated merely by a bifid pelvis. The division is usually unequal as it is the superior calix that tends to separate from the remainder of the pelvis. It often occurs as an almost normal variant (*i.e.* 10% of the population) (Campbell, 1963).

The anomaly described here may be explained by further migration of the ureteric bud into the surrounding renal blastema following its division into a bifid pelvis. The superior calix will drain the corresponding upper half of the kindey through a narrow long pelvis into the middle calix or the

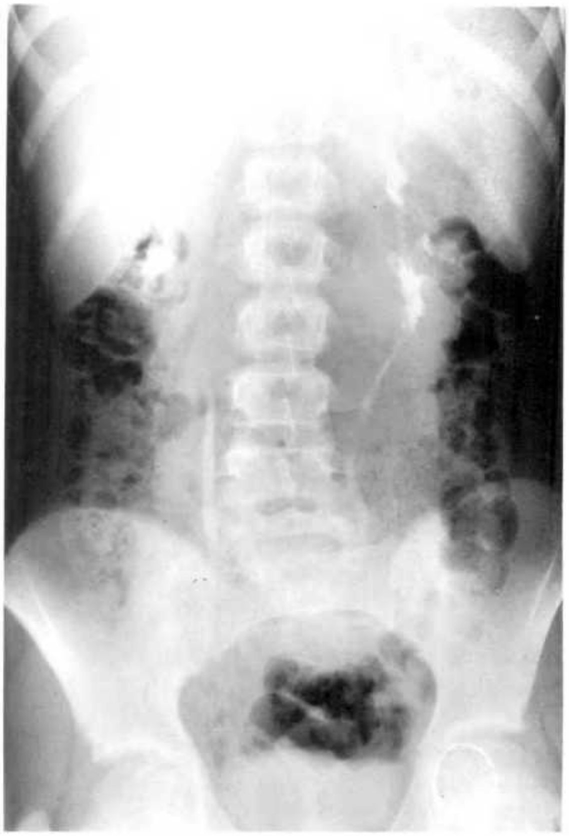

Fig. 1 IVU showing intrarenal duplication.

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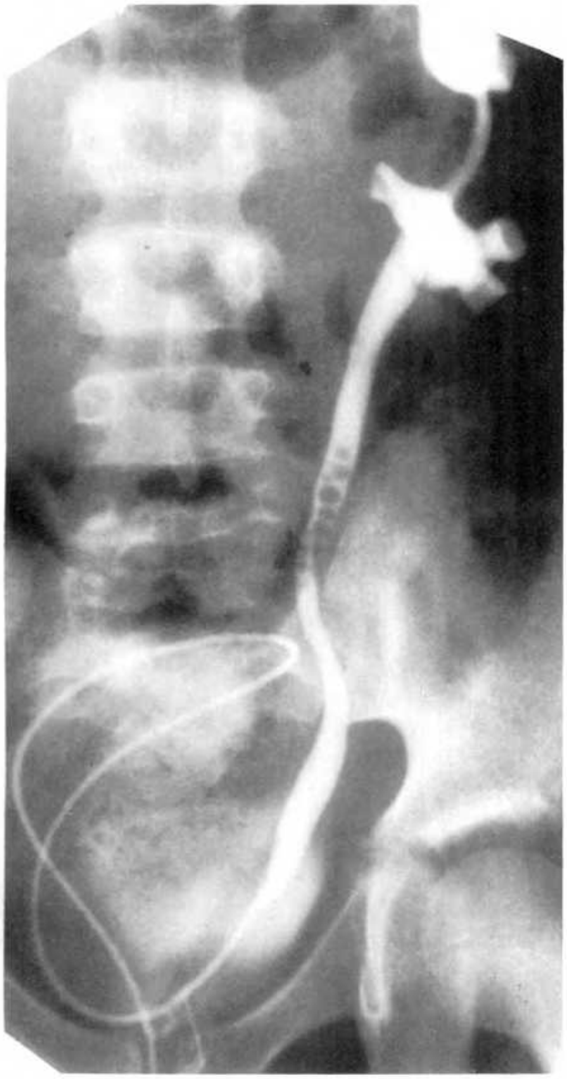

Fig. 2 Retrograde pyelogram showing intrarenal duplication.

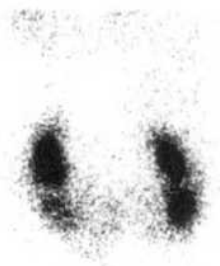

Fig. 3 ^{99m}Tc DMSA showing demarcation between two halves of the kidneys.

lower pelvis with a single extrarenal ureter, depending on the degree of intrarenal migration (Fig. 4).

Although the bifid pelvis is the commonest form of renal duplication (Ambrose, 1972), we believe that intrarenal duplication has not been described before.

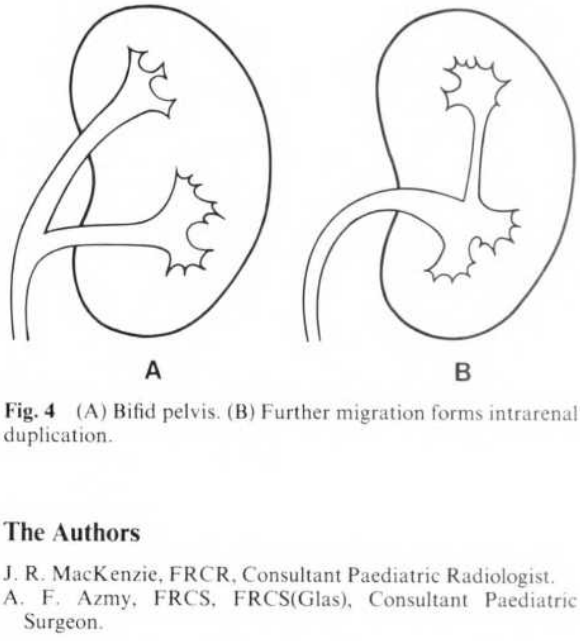

Fig. 4 (A) Bifid pelvis. (B) Further migration forms intrarenal duplication.

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Absence of Peripheral-type Benzodiazepine Binding Sites in Renal Carcinoma: a Potential Biochemical Marker

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Summary—In an attempt to identify a tumour marker, we investigated peripheral-type benzodiazepine binding sites (PBS) in kidney specimens obtained from patients who underwent nephrectomy due to a renal mass. [^{3}H]PK 11195, an isoquinoline carboxamide derivative, was used as a ligand. Binding assays were conducted on samples of membrane homogenate taken from both the healthy portion and the tumour site of the kidney. It was found that binding characteristics of benign tumours and normal kidney tissues were not significantly different, *i.e.* equilibrium dissociation constants of 2.20 ± 0.73 and 2.38 ± 0.98 nM, respectively, and maximal number of binding sites of 3190 ± 1081 and 4189 ± 998 fmol/mg protein, respectively. In contrast, no PBS were detectable in renal carcinoma. The absence of PBS in malignant renal tissues may serve as a biochemical marker for tumours of the kidney.

The pharmacological function of benzodiazepines (BZ) is mediated through a specific macromolecular receptor complex located in the central nervous system. In addition, another type of BZ binding sites has been demonstrated in various peripheral tissues (Marangos *et al.*, 1982) and is referred to as PBS. These sites exhibit high affinity for the BZ ligand Ro 5-4864 and for PK 11195, a non-BZ isoquinoline carboxamide derivative, both of which are not bound by the central receptors.

Although the exact function of PBS has not yet been fully determined, evidence suggests that they play a role in cardiac function (Mestre *et al.*, 1984), in the pathogenesis of hypertension (Taniguchi *et al.*, 1981) and in renal water and salt balance (Regan *et al.*, 1981; Del Zompo *et al.*, 1984). PBS have been identified in cultures of normal and malignant cell lines, and the presence of BZ ligands in the medium can modulate the proliferative, differentiative and intracellular processes of the cultured cells (Clark and Ryan, 1980; Wang *et al.*, 1984).

Renal carcinomas represent approximately 1% of all malignancies except skin cancer (Deming and Harvard, 1970). Three cell types have been identified in renal carcinoma: clear cells, granular cells and sarcomatoid cells (Sun *et al.*, 1977). Benign renal tumours include xanthogranulomatous pyelonephritis, angiolipomas and, primarily, adenomas; the latter are usually asymptomatic and found on autopsy. However, it is often difficult to distinguish histologically between benign and malignant tumours. No biological marker associated with renal neoplasms has yet been found. In an attempt to identify such a marker, peripheral benzodiazepine binding sites (PBS) were investigated in normal human kidney, benign renal tumours and renal carcinoma.

Patients and Methods

Subjects

The study included 8 patients (4 men and 4 women; mean age 66.8 years; range 61–74) who were diagnosed by clinical symptoms and X-ray findings

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Table Binding Characteristics of [^{3}H]PK 11195 to Membranes from the Healthy Portion of the Kidney, Benign Renal Tumours and Renal Carcinomas

Patient no	*Age/sex*	*Additional disorders*	*Type of tumour*	*Binding characteristics*			
				Healthy portion		*Tumour site*	
				K_D	B_{max}	K_D	B_{max}
1	63 F	Hypertension	Oncocytoma	2.25	2862	3.55	5525
2	66 M	IHD Diabetes	Oncocytoma	1.42	3523	1.87	3420
3	74 M	CHF	Oncocytoma	3.20	5254	2.77	4381
4	63 F	Hypertension	Xanthogranulomatous pyelonephritis	1.77	2163	1.32	3430
5	61 F	None	Renal carcinoma	1.53	2056	—	—
6	64 F	Arthritis, hypertension	Renal carcinoma	2.39	3155	—	—
7	72 M	IHD Status after thyroidectomy	Renal carcinoma	1.73	4074	—	—
8	71 M	None	Renal carcinoma	3.30	2431	—	—

IHD: Ischaemic heart disease CHF Congestive heart failure, — Absence of specific binding K_D: Equilibrium dissociation constant (nM) B_{max}. Maximal number of binding sites (fmol/mg protein)

as having a renal mass. Most had additional disorders such as hypertension, ischaemic heart disease or diabetes mellitus (Table). None of the patients who participated in the study received any pre-operative hormonal treatment. Each subject gave written informed consent and the study was approved by the Helsinki Committee of our institution.

Preparation of the membranes

The specimens were obtained post-operatively. Each kidney was cut horizontally into 2 equal parts and 2 samples (1 cm^3), 1 from the centre of the tumour and 1 from the apparently healthy cortical portion of the kidney (which was used as a control), were removed and immediately frozen at −20°C. Samples with a high degree of necrosis were not included in the study. The type of tumour was later confirmed by pathological examination. Before the binding assay, tissues were thawed and homogenised in 100 volumes of 50 mM Tris-HCl buffer, pH 7.4, at 4°C by a Brinkmann Polytron (setting 10) for 20 s. The homogenate was centrifuged at 49,000 × *g* for 15 min, and the pellet was resuspended in 200 volumes of Tris-HCl buffer as described above and filtered through cotton gauze to remove coarse particles.

[^{3}H]PK 11195 Binding assay

[^{3}H]PK 11195 (New England Nuclear, Boston, USA) binding was conducted as previously described (Gavish *et al.*, 1987). Binding assay in a final volume of 500 µl contained 400 µl membranes of kidney (110–200 µg protein) and 25 µl [^{3}H]PK 11195 (final concentration 0.2–6 nM) in the absence (total binding) or presence (non-specific binding) of 1 µM unlabelled PK 11195 (kindly donated by Dr G. Le Fur, Pharmuka Laboratories, Gennevilliers, France). After incubation for 60 min at 4°C, samples were filtered under vacuum over Whatman GF/B filters and washed 3 times with 3 ml Tris-HCl buffer. Filters were placed in vials containing 4 ml xylene/Lumax (v/v, 3:1) (Lumac, Schaesberg, The Netherlands) and counted for radioactivity after 12 h.

Statistical analysis

Results are expressed as mean ± SD. The data were analysed by means of Student's *t* test.

Results

The equilibrium dissociation constant (K_D) and the maximal number of binding sites (B_{max}) of PBS in the healthy portion of the kidney, in benign renal tumours and in renal carcinoma were determined from saturation curves of [^{3}H]PK 11195 binding by Scatchard analysis (Table).

The mean K_D and B_{max} values in the healthy portion of the kidney were 2.20 ± 0.73 nM and 3190 ± 1081 fmol/mg protein, respectively. The mean K_D and B_{max} values in benign renal tumours were 2.38 ± 0.98 nM and 4189 ± 998 fmol/mg protein, respectively. Thus there were no significant differences in binding properties of PBS in the healthy portion of the kidney and in benign renal tumours. Representative Scatchard plots of satura-

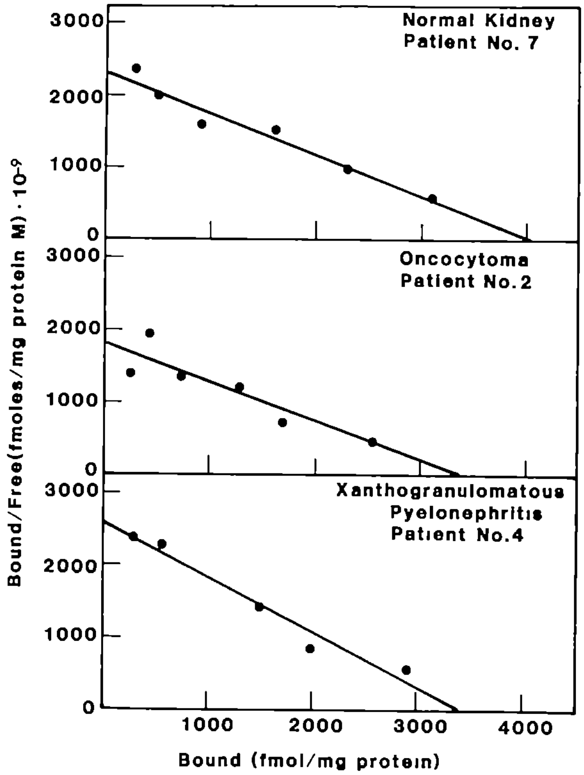

Fig. Representative Scatchard plots of [^{3}H]PK 11195 binding to membranes from healthy portion of the kidney and benign renal tumours.

tion curves of [^{3}H]PK 11195 binding to these tissues are presented in the Figure.

There was a total absence of demonstrable PBS in all malignant kidney membranes tested (Table).

Discussion

The exact physiological role of PBS in the kidney is unknown. PBS are hormone-regulated and have been localised by autoradiography in the ascending loop of Henle and the distal convoluted tubule, which is an aldosterone-sensitive structure (Gelhert *et al.*, 1985). A significant reduction in the density of PBS in rat kidney following adrenalectomy has been reported (Basile *et al.*, 1985), reversible by aldosterone but not by dexamethasone. Increases in the density of PBS in rat kidney occur following prolonged progesterone and thyroxine treatment (Gavish *et al.*, 1986, 1987) and in kidneys of deoxycorticosterone/salt-hypertensive rats (Regan *et al.*, 1981) as well as those of the Brattleboro rat, an animal model of diabetes insipidus (Del Zompo *et al.*, 1984). However, a decrease in platelet and renal PBS has been observed in spontaneously hypertensive rats compared with controls (Taniguchi *et al.*, 1981). In our study, the kidneys of patients with hypertension demonstrated binding properties similar to those of healthy controls.

The main finding in this investigation was the absence of PBS in renal carcinoma. Recent studies have demonstrated that PBS are part of the mitochondrial outer membrane and are closely related to cytochrome oxidase activity (Anholt *et al.*, 1986). The loss of binding characteristics in the malignant tumours is probably due to changes in the structure of the neoplastic cell and its organelles. An electron microscopic study of human renal adenocarcinoma demonstrated sparse to numerous mitochondria in the malignant cells (Fisher and Horvat, 1972). Our observations indicate that these mitochondria may be abnormal, in that they cannot bind the peripheral BZ ligand, but this needs further investigation.

The absence of BZ binding sites in a malignant renal tumour could serve as a biochemical marker in the pre-operative evaluation of patients if binding assays are performed on renal biopsy specimens, since preliminary rapid binding assays can easily be made. As with other marker systems, there may be false-positive and false-negative results, and PBS binding should be evaluated in a larger number of benign and malignant renal samples.

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Unexplained Spontaneous Regression and Alpha-interferon as Treatment for Metastatic Renal Carcinoma

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Summary—A series of 73 patients with measurable metastatic disease referred to a tertiary referral centre for consideration for an experimental treatment protocol were entered into a surveillance protocol in order to establish the incidence of spontaneous regression. Initially, patients were taken off the study if metastases showed >25% increase in products of bidimensional measurement but with increasing confidence patients went into therapy protocols only following the development of symptomatic progression. We observed 3 complete and 2 partial unexplained spontaneous regressions and a further 4 patients had prolonged stable disease for more than 12 months.

A group of 21 patients on progression subsequently received treatment with alpha-interferon (Wellferon) as part of a multicentre study which included an additional 61 cases; 12 responded (3 surveillance relapse patients and 9 others). Patients with lung metastases only had the highest response rate (10/17 compared with 5 unexplained responses seen in 38 such patients on surveillance). These results confirm that alpha-interferon is active against metastatic renal carcinoma and that the responses are not totally explicable by spontaneous regression.

Over the last 20 years there has been a waxing and waning of enthusiasm amongst clinicians treating renal carcinoma for a wide range of treatments (hormones, chemotherapy, specific and non-specific tumour vaccines, interferon and, most recently, interleukin-2 combined with lymphokine-activated killer cells). It has long been known that renal carcinoma has a particularly high frequency of unexplained spontaneous regression (Everson and Cole, 1966) and it has been suggested that this could contribute to the difficulty in determining the results of treatment trials if selection resulted in variable proportions of patients with a favourable prognosis being treated. Despite conflicting reports from retrospective studies, however, there has been no attempt to establish the frequency prospectively. In an attempt to rectify this deficit, a phase 1/2 study of surveillance of patients with metastatic renal carcinoma prior to entry into a treatment protocol was undertaken and preliminary results reported (Oliver *et al.*, 1988). This revealed a 7% incidence of unexplained spontaneous response. The present report extends these observations and focuses on patients who, on progression from this study, received alpha-interferon (Wellferon) as part of a multicentre study and compares their response with that of patients who did not have the preliminary period of surveillance.

Patients and Methods

Surveillance study

All patients referred to R.T.D.O. between September 1977 and May 1987 had a preliminary period of observation with radiological and biochemical investigations repeated monthly until progression of their disease.

Initially, all patients who had clinical sympto-

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

matic progression or >25% increase in the size of metastases without symptoms left the study, but with increasing experience in the safety of this approach all patients, as long as they remained asymptomatic, remained under observation until they developed >50% increase in measurable metastases.

Treatment of surveillance patients on progression

Prior to participation in the interferon studies, patients received either intradermal BCG (Glaxo) weekly for 4 weeks and then monthy, or entered into a multicentre study of mitozantrone at 1 of 2 doses, either 12 mg/m^2 3-weekly or 4 mg/m^2 × 5 3-weekly.

Alpha-interferon (Wellferon) studies

Two principal schedules of treatment were investigated: firstly, 2.5 mega units/m^2 daily for 5 days a week until progression of disease. If patients developed toxicity, the treatment was reduced to alternate days or 3 days a week. The second schedule was an escalating dosage schedule, starting at 5 mega units/m^2 daily for 7 days and then escalating, providing the patient tolerated treatment, by 5 mega units/m^2 on the first day of each subsequent week up to a maximum of 30 mega units/m^2. Patients could subsequently be maintained on the maximum tolerated dose if responding.

In addition to these schedules, a miscellaneous group of patients received a lower dose of 3 mega units thrice-weekly or thereabouts.

Results

A total of 73 patients were entered into the surveillance study and 5 (7%) demonstrated an episode of unexplained spontaneous regression (3 complete responses (CR) and 2 partial responses (PR) lasting 10, 52, 120, 4 and 42 months). On progression, 52 were entered into specific therapy studies and a further 7 (14%) demonstrated evidence of tumour regression (2 complete remissions and 5 partial remissions lasting 3, +84, 5, 13, 18 and 24 months).

Although there were 4 additional patients in the surveillance study and a further 4 on treatment who showed prolonged disease stabilisation for 14, 30, +36, 48 and 13, +18, 24 and +30 months, most patients progressed within 1 to 3 months (Table 1). There was a suggestion that disease progression was somewhat less rapid in patients when they had been entered into the studies of therapy than when the same patients were on surveillance, though this was not statistically significant.

Table 1 Progression Rate (%) of Metastatic Renal Carcinoma on Surveillance and Therapy

	1 Month	*3 Months*	*12 Months*
Surveillance (n = 73)	40	74	90
Therapy (n = 52)	29	50	86

A total of 82 patients were entered into the multicentre Wellferon study (Table 2).

Three of 21 patients (14%) who were part of the surveillance study and 9 of 61 (15%) of the remaining patients responded to treatment. There was no difference in the response rate between the two schedules (Table 3). The only significant difference in response rate was seen when the incidence in patients with lung metastases as the sole site of disease was compared with the incidence in patients with metastases at any other combination of sites of disease (Table 4). Furthermore, the incidence of regression in the group of patients with lung metastases only who were receiving Wellferon was also significantly higher than the incidence of spontaneous unexplained regression in the similar group of patients on surveillance.

Discussion

There can be little doubt that selection of patients for referral to a tertiary treatment centre means that the frequency of spontaneous unexplained regressions in this series is likely to be higher than that occurring in the disease as a whole. Since it is patients such as these who would be referred for new experimental treatments, however, they do indicate the upper limit of what can be explained on the basis of this phenomenon. The fact that on treatment with interferon the response rate was double that seen on surveillance suggests that there is a genuine therapeutic advantage in giving interferon. Furthermore, there is no apparent loss of responsiveness in patients with disseminated disease by first observing them to exclude those who might undergo spontaneous unexplained regression. However, for patients with disease limited to the lungs it may be preferable to begin interferon treatment before wider dissemination of disease occurs, since optimal response rates appear to occur in this subgroup. Given the universal reproducibility of response to interferon (12–25%) in all studies reported to date (Kirkwood and Ernstoff, 1984), it must be concluded that interferon

Table 2 Wellferon Clinical Trials in Renal Carcinoma

Dosage schedule	*Median duration (weeks)*	*Average dose (mega units/week)*
2 5 mega units/m^2/daily × 5/week (n = 34)	15	25
6 weeks escalating 5–30 mega units/m^2 (n = 31)	7	108
3 mega units thrice weekly (n = 17)	10	10

Table 3 Alpha-interferon Clinical Trials in Renal Carcinoma

	CR + PR (%)	*Duration (months)*
2 5 mega units/m^2/daily × 5/week (n = 34)	0 + 5 (15)	3, 7, 8, 8, 18
6 weeks escalating 5–30 mega units/m^2 (n = 31)	2 + 4 (19)	+ 1, 2, 3, 4, 5, 18
< 2 5 mega units/m^2 daily × 5/week (n = 17)	0 + 1 (6)	4
All patients (n = 82)	2 + 10 (15)	—

is the first agent in this disease to have a response rate which is higher than the spontaneous unexplained regression rate. Since the selection criteria for entry into the highly toxic interleukin-2/lymphokine-activated killer cell therapy programmes are more exacting (Rosenberg *et al.*, 1987; West *et al.*, 1987; Fisher *et al.*, 1988), it would be premature to conclude that the present higher response rate for IL-2/LAK is genuine, without more information on spontaneous regression rates in the type of patient who would be eligible for these programmes.

It is unfortunate that the overall response rate for interferon has not been improved by the more intensive short-term escalating schedule which has been explored in the multicentre study. However, in view of the higher response rate documented in patients with small-volume lung disease without other sites of metastases, it is possible that there might be a proportionately higher benefit from the use of interferon in the adjuvant setting. Possible support for this concept has come from recent studies in an experimental mouse metastasis model. Ramani *et al.* (1986) reported a considerable increase in therapeutic effect by giving treatment at the time of direct inoculation of tumour cells in the blood stream which could not be demonstrated if there was more than a few days' delay after starting the interferon. Were handling of tumour prior to surgical excision to be a factor in metastatic spread, such short-term peri-operative treatments could be very cost-effective approaches to the use of interferon which might have widespread application across the whole field of surgery. Currently, 8 patients have undergone nephrectomy without problems after pre- and post-operative interferon in a pilot study to establish the safety of such an approach prior to setting up a formal randomised study.

Though it can occasionally be difficult to distinguish a renal carcinoma from extensive local invasion by renal pelvic transitional cell carcinoma pre-operatively, the demonstration that interferon may have some activity against transitional cell tumours in the renal pelvis (Torti and Lum, 1984; Oliver *et al.*, 1986) provides some justification for including all patients with a suspicious renal mass. Because of a recent report of apparent accelerated growth in patients with poorly differentiated superficial bladder cancer following treatment with interferon (Ackerman *et al.*, 1987), possibly related to imbalance of MHC antigen expression as seen in animal tumours (Eisenbach *et al.*, 1983), this study is limited to patients with established metastases who are candidates for nephrectomy. Within this context, the administration of interferon at a dose of 3 mega units for 3 days before and 10 days

Table 4 Influence of Site of Metastases on Unexplained and Post-alpha-interferon Response

	CR + PR (%)
Lung only	
Surveillance study (n = 38)	3 + 2 (13)
Wellferon (n = 17)	2 + 8 (59)
Other sites ± lung	
Surveillance study (n = 35)	0 + 0 (–)
Wellferon (n = 64)	0 + 2 (3)

after operation appears, on preliminary experience to be a safe and acceptable approach.

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Leiomyosarcoma of the Kidney. Immunohistological and Ultrastructural Findings with Special Emphasis on the Growth Fraction

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Summary—This report deals with a case of renal smooth muscle tumour. Considering the low mitotic rate, this neoplasm would have been classified as leiomyoma. However, it displayed a relatively large growth fraction by immunostaining with the monoclonal antibody Ki-67. This led us to the diagnosis "leiomyosarcoma", which is in line with the unfavourable clinical course. We suggest that assessment of the growth fraction with Ki-67 seems to be more objective than the conventional criteria for determining the malignant potential of smooth muscle tumours.

Leiomyosarcomas are predominantly tumours of adult life and account for about 7% of soft tissue sarcomas. The most common subgroup comprises retroperitoneal and intra-abdominal leiomyosarcomas (Enzinger and Weiss, 1983). Leiomyosarcomas have also been associated with vessels in a number of parenchymal organs. However, a survey of the literature reveals only 84 cases of renal leiomyosarcoma (Nair and Thomas, 1977; Schindler *et al.*, 1980; Chrisogonidis and Gockel, 1981; Selli *et al.*, 1982; Brenner, 1983; Ng *et al.*, 1985). The establishment of suitable criteria to characterise the biological behaviour of smooth muscle tumours is difficult. Unfortunately, even when criteria of conventional morphology are employed, such as cell size, cellularity, atypia, necrosis and mitotic activity, it is never possible to be certain about the biological behaviour of these neoplasms (Enzinger and Weiss, 1983). We describe a case of renal smooth muscle tumour and introduce immunohistological methods for determining the growth fraction in order to shed some light on its biological behaviour.

Case Report

Clinical findings

In a 65-year-old male patient with no major complaints and an uneventful previous clinical history, a routine check-up revealed a large mass at the upper pole of the right kidney. Laboratory investigations were in the normal range. Following a CT scan, nephrectomy was performed with the clinical diagnosis of renal adenocarcinoma. The clinical follow-up 6 weeks post-operatively showed progressive swelling of the mediastinal lymph nodes, which were biopsied. Histological examination revealed lymph node metastases. The patient is still alive but his condition is slowly deteriorating due to progression of the malignant process.

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Morphological findings

Macroscopic appearance. The tumour (diameter 10 cm, weight 150 g) was situated at the upper pole of the kidney but was not apparently attached to neighbouring structures such as the renal pelvis or blood vessels. It showed a greyish lobulated aspect on the cut surface, was of firm consistency and seemed to be encapsulated (Fig. 1).

Light and electron microscopy. The relatively monomorphic tumour cells were medium-sized, elongated and had abundant cytoplasm. Most of the centrally located nuclei displayed blunt poles and a large nucleolus (Fig. 2, inset). The mitotic rate amounted to less than 1% of the tumour cell population (3 mitoses/10 high power fields). The cells were composed of fascicles intersecting each other at right angles. Moreover, this tumour exhibited sharply marginated borders with a small fibrous capsule (Fig. 2) and extensive hyalinisation was conspicuous in the central parts.

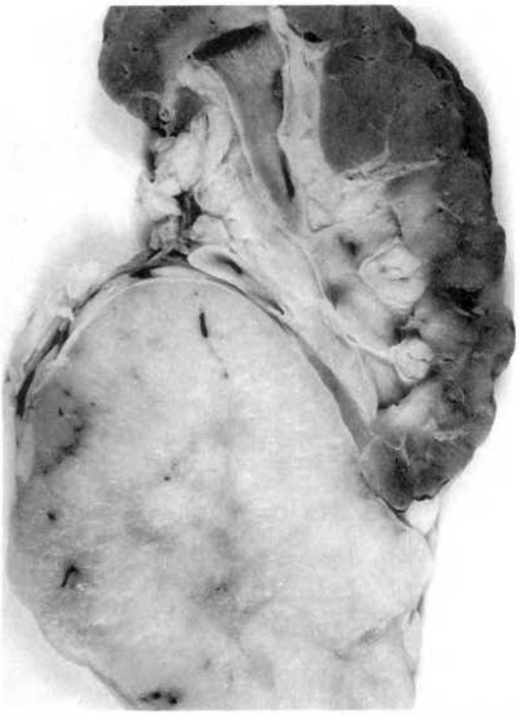

Fig. 1 Mesenchymal renal tumour, lobulated, whorled and encapsulated on cut surface.

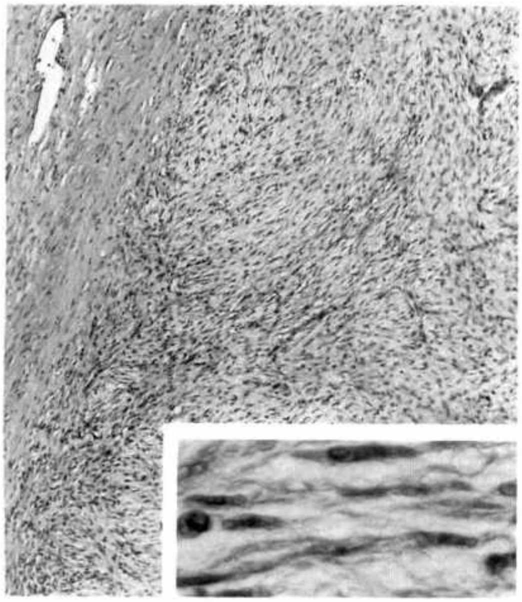

Fig. 2 Mesenchymal renal tumour. Fibrous capsule as margination of tumour. Inset: monomorphic tumour cell with blunt-ended, centrally located nuclei. No mitoses. (H and E ×65. Inset ×260).

On electron microscopic examination a number of distinctive ultrastructural features were observed. Several cells had deeply cleft nuclei, large nucleoli and numerous well orientated thin filaments. Intercellular connections were numerous and basal lamina-like material surrounded the entire cell membrane. On the other hand, some cells showed a loss of filaments and the rough endoplasmic reticulum and free ribosomes assumed greater prominence. The plasma membrane displayed many small, dense, elevated areas, probably remnants of the former anchoring sites of myofilaments.

Immunhistology. As demonstrated in Figure 3, the vast majority of tumour cells were positive with the antibody DE-R-11 (Debus *et al.*, 1983), which is directed against desmin, the characteristic intermediate filament of muscles (Altmannsberger *et al.*, 1982). There was a positive reactivity with V9 (Osborn *et al.*, 1984), which recognises intermediate filament vimentin. Staining with different anti-cytokeratin antibodies yielded negative results. In contrasts to the low mitotic rate found in conventional histology, staining with Ki-67 (directed against a proliferation-associated nuclear antigen) (Gerdes *et al.*, 1984) revealed a growth fraction of more than 8% (Fig. 4). Ki-67 positive tumour cells as well as all tumour cells were counted with the help of a calibrated grid on an area of 1.2 mm^2.

Discussion

Light and electron microscopic findings, together with the immunohistological demonstration of

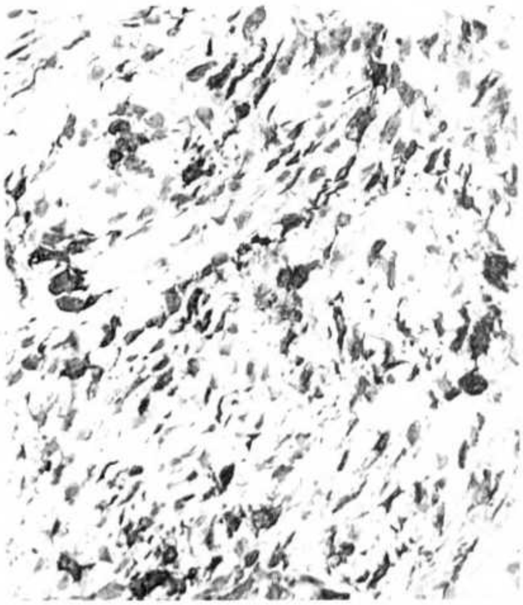

Fig. 3 Positivity of tumour cells for DE-R-11, an antibody directed against desmin: sections from paraffin embedded blocks. (APAAP ×120).

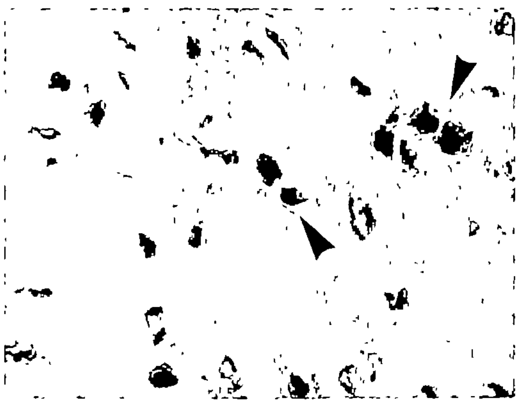

Fig. 4 Assessment of growth fraction with Ki-67, an antibody directed against a proliferation-associated nuclear antigen. sections from fresh frozen tissue Some positive nuclei are marked with arrowheads. (APAAP ×350)

desmin, indicated that the tumour was derived from smooth muscle cells. The positive reactivity with the tumour cells for vimentin was not in conflict with this statement, since vimentin can be found in the smooth muscle cells of small vessels (Gabbiani *et al.*, 1981b; Osborn *et al.*, 1984) and also in smooth muscle cells at various stages of their development (Bennet *et al.*, 1979; Gard and Lazarides, 1980). Moreover, there have been reports about double expression of both intermediate filament antigens in leiomyomas and leiomyosarcomas of the uterus (Gabbiani *et al.*, 1981a; Due *et al.*, unpublished results).

On the basis of its low mitotic rate, together with the other histological and cytological features, this neoplasm would have been classified as a leiomyoma. However, the elevated growth fraction measured by immunostaining with the antibody Ki-67 suggested that it was malignant and thus led to the diagnosis of leiomyosarcoma.

This diagnosis is borne out by the unfavourable clinical course of the patient, in whom mediastinal lymph node metastases were clinically apparent a few weeks after nephrectomy and confirmed histologically; the patient's condition then rapidly deteriorated. Thus we conclude that the assessment of growth fraction with the antibody Ki-67 is more objective than conventional methods for determining the malignant potential of smooth muscle tumours. This preliminary conclusion needs to be confirmed by studying a large series of apparently well differentiated smooth muscle tumours. Since the determination of the growth fraction in these neoplasms appears to be of prognostic value, it may become an important aid in choosing appropriate therapy (Beccia *et al.*, 1979).

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Transitional Cell Carcinoma of the Renal Pelvis and Ureter

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Summary—In a retrospective study of 185 patients with transitional cell carcinoma of the renal pelvis and ureter, of whom 127 were treated by total nephroureterectomy and 58 by conservative resection, the survival of those with superficial well differentiated tumours was >90% in each group. When urothelium was left behind after conservative resection, there was a 22% rate of recurrence on the same side but this almost only occurred when the original tumour had been multifocal. Post-operative radiotherapy did not improve survival.

The conventional treatment for urothelial cancer of the renal pelvis and ureter has been total nephroureterectomy with removal of a cuff of bladder, but for many years the need for this has been questioned (Vest, 1945) and conservative resections for tumours in the renal pelvis and ureter have been increasingly advocated. This policy is not in dispute when the general condition of the patient precludes nephroureterectomy, or when there is a high risk of bilateral tumours and impaired renal function (Petkovic, 1972). If the indications for conservative resection are to be further extended, however, it is necessary to be sure that the survival of the patient is not thereby put at risk, and equally necessary to quantify the chance of recurrence in order to plan adequate follow-up. Tumours of the upper tract are uncommon and none of the reported series has so far provided clear guidelines on either issue—survival or chance of recurrence. The present study, which combined the experience of 3 hospitals, set out to examine these questions.

Patients and Methods

Records of 185 cases of transitional cell carcinoma of the renal pelvis and ureter were examined in 3 centres (The London Hospital 1966–1986 (88); Whipps Cross Hospital 1970–1986 (45); St Peter's Hospitals 1978–1985 (52)). All patients were followed by regular check cystoscopy and urography; 4 patients were referred back to other hospitals and were lost to follow up after 2 years; the remainder have been followed until death (mean follow-up period 6.4 years.)

The site of the upper tract tumours, and whether they were solitary or multifocal, was noted from the radiological, operative and pathological description. Tumours were graded and staged according to the UICC (1978) as adapted by Auld *et al.* (1984) with the exception that, since in practice the UICC stages pT2 and pT3 cannot be distinguished in the thin muscle layer of the upper tract, they have been combined for the purpose of this study.

Treatment

A series of 127 patients underwent classical total nephroureterectomy with excision of a cuff of bladder. In 58 patients some form of conservative resection was performed, 33 patients underwent nephrectomy without removal of the entire ureter either because standard total nephroureterectomy with removal of a cuff of bladder was contraindicated by the age or physical debility of the patient, or because the tumour was so extensive that such an addition to the operation would have been futile.

Post-operative radiotherapy was given to the renal or ureteric bed in 23 patients, mainly with

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invasive or poorly differentiated tumours, in varying doses from 3000 to 5000 cGy.

Statistical methods

Survival was calculated using the life-table method (Kaplan-Meier experimental survival curves) and the Institute of Urology computer package (Hill, 1979).

Results

The mean age at presentation was 63 years (range 28–93) and males outnumbered females 3:1 (Fig. 1).

More than half of these upper tract tumours were in the renal calices or pelvis and most of them had not invaded muscle (Table 1). The small difference in the tumour stages in the groups treated by total or conservative resection is accounted for by the group with very advanced tumours, where only simple nephrectomy was performed (Table 2). Whether they were treated by total or conservative resection, the original upper tract tumours showed a similar proportion of tumour grade (Table 3) and about the same proportion of original upper tract tumours was multifocal in each group (Table 4).

Survival

The 5-year actuarial survival rate for the whole group was 80%: within this global figure there were

Table 1 Tumour Stage in 185 Upper Tract Urothelial Cancers

Stage	*Pelvis*	*Pelvis and ureter*	*Upper ureter*	*Lower ureter*	*Whole ureter*	*Total*	*%*
pTa, pT1	67	17	9	24	2	119	64.3
pT2+3	11	2	4	11	2	30	16.2
pT4	23	8	2	1	0	34	18.4
pX	0	0	1	1	0	2	1.1
Total	101	27	16	37	4	185	
%	54.6	14.6	8.6	20	2.2		

Table 2 Total or Conservative Resection and Tumour Stage

	pTa/pT1 (%)	*pT2/pT3 (%)*	*pT4 (%)*	*pTx (%)*	*Total*
Nephroureterectomy	83 (65.3)	23 (18.1)	19 (15.0)	2 (1.6)	127
Conservative					
Nephrectomy and partial ureterectomy	15	3	15	—	33
Partial nephrectomy	2	—	—	—	2
Localised excision and anastomosis	5	2	—	—	7
Lower ureterectomy and reconstruction	14	1	—	—	15
Hemi-nephroureterectomy	—	1	—	—	1
	36 (62.1)	7 (12.1)	15 (25.8)		58
Total	119	30	34	2	185

Table 3 Operations and Tumour Grade

	G1 (%)	*G2 (%)*	*G3 (%)*	*Total*
Nephroureterectomy	52 (40.9)	58 (45.7)	17 (13.4)	127
Conservative operations				
Nephrectomy with partial ureterectomy	8	15	10	33
Partial nephrectomy	2			2
Localised excision and end-to-end anastomosis	4	3		7
Lower ureterectomy and reconstruction	11	4		15
Hemi-nephroureterectomy	—	1		1
	25 (43.1)	23 (39.7)	10 (17.2)	58
Total	77 (41.6)	81 (43.8)	27 (14.6)	185

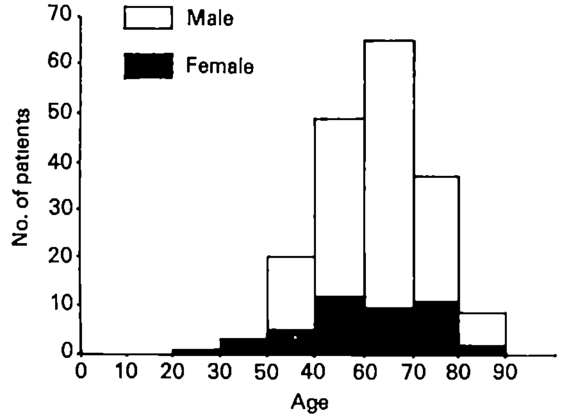

Fig. 1 Mean age at presentation

Table 4 Single and Multifocal Tumours

	Single (%)	*Multifocal (%)*
Nephroureterectomy	73 (57.5)	54 (42.5)
Conservative resections	34 (58.6)	24 (41 4)

considerable variations according to tumour grade (Fig. 2) and stage (Fig. 3). Undifferentiated tumours and those which invaded muscle had a poorer prognosis.

Total versus conservative resection

Although the survival figures seemed to show a trend in favour of total nephroureterectomy compared with conservative resection when tumours were G2 or G3 (Fig. 4, Table 5) or when muscle was invaded (Table 6), this did not reach statistical significance.

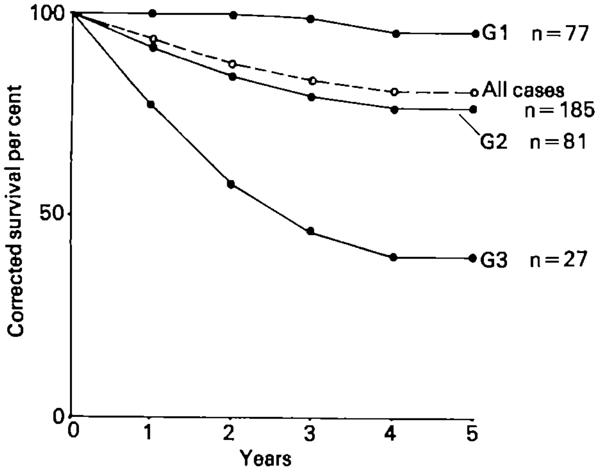

Fig. 2 Survival and tumour grade.

Table 5 Total versus conservative Resection and Tumour Grade (5-year corrected survival)

	Nephroureterectomy		*Conservative resections*		*All cases*	
	No	*%*	*No*	*%*	*No*	*%*
G1	52	95	25	100	77	97
G2	58	82	23	62	81	76
G3	17	54	10	0	27	40

Table 6 Five-year Actuarial Survival and Tumour Stage (5-year corrected survival)

	Nephroureterectomy		*Conservative resections*		*All cases*	
	No	*%*	*No*	*%*	*No*	*%*
pTa	38	90	19	100	57	94
pT1	45	95	17	100	62	96
pT2/3	23	85	7	70	30	80
pT4	19	38	15	12	34	27

Radiotherapy

The survival curves for patients who underwent post-operative radiotherapy for G3 or pT4 tumours are shown in Figures 5 and 6. In this selected series there was no obvious improvement in survival following adjuvant post-operative radiotherapy.

Recurrence

Bladder tumours. Of 185 patients treated for upper tract tumours, 64 (34.6%) had either suffered from a previous bladder tumour or developed one in the follow-up period (Table 7).

Recurrence in the upper tract on the same side. Of the 58 patients who underwent conservative resection, 13 (22.4%) developed another tumour of the urothelium on the same side as the original one. The site of the original tumours was not important—the crucial feature was whether they had been solitary or multifocal (Table 8). Only 1 of 34 (3%) of those whose first tumour was solitary developed a recurrence in the urothelium left behind on that side, in contrast to 12 of 24 (50%) whose tumours were originally multifocal.

Local and regional recurrence. Only 4 of the 185 patients (2.2%) developed local or regional recurrence: 1 after conservative resection (1.7%) and 3 after total nephroureterectomy (2.4%). Total removal did not affect the rate of local recurrence.

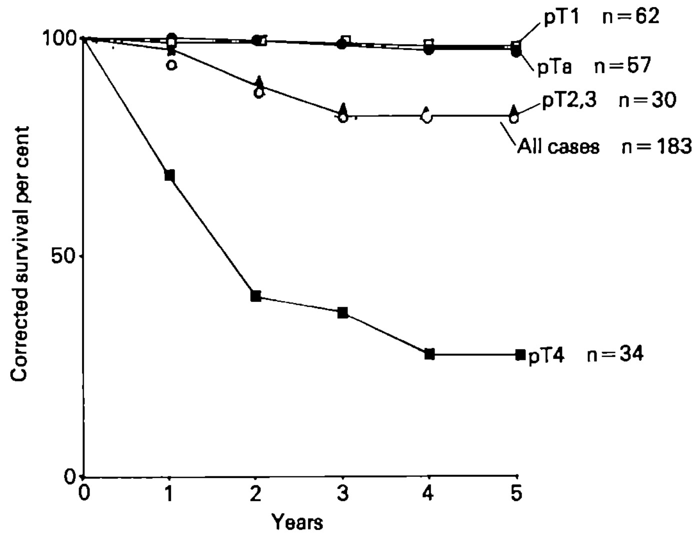

Fig. 3 Survival and stage

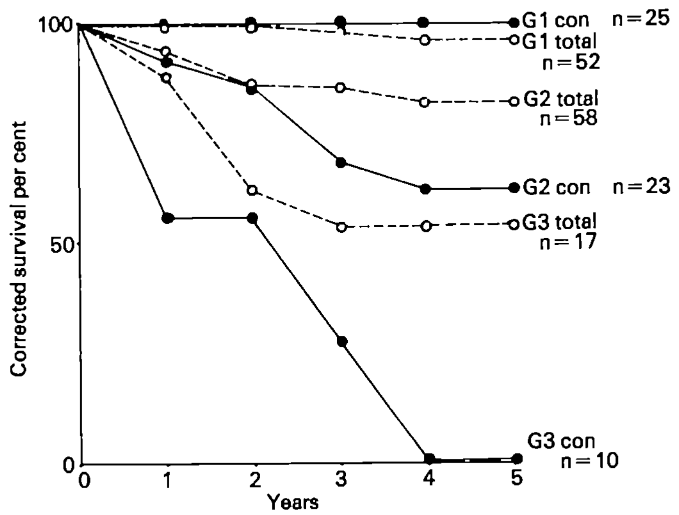

Fig. 4 Total nephroureterectomy versus conservative resection Survival and tumour grade.

Table 7 Upper Tract and Bladder Tumours

	No.	%
Previous or co-existent	31	16.8
Subsequent	33	17.8
No bladder tumour	121	65.4
Total	185	

Bilateral tumours. None of these patients presented with bilateral upper tract tumours. A tumour developed on the other side in the course of follow-up in 3 of 185 patients (1.6%) and in 2 of these the original tumour was multifocal.

Discussion

The importance of tumour grade and stage has been well documented for upper tract urothelial tumours (Mazeman, 1976; Rubinstein *et al.*, 1978; Booth *et al.*, 1980; Kjaer *et al.*, 1981; Zincke and Neves, 1984) but these authors reached conflicting conclusions in respect of survival and tumour grade, stage and site.

With numbers which allow the use of the actuarial life-table method the present study has shown the following:

(i) Tumour grade and stage is far more important than the extent of surgical resection.

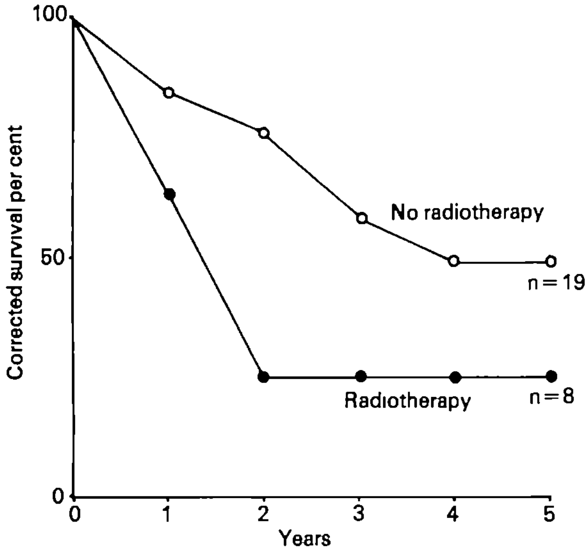

Fig. 5 G3 tumours and post-operative radiotherapy

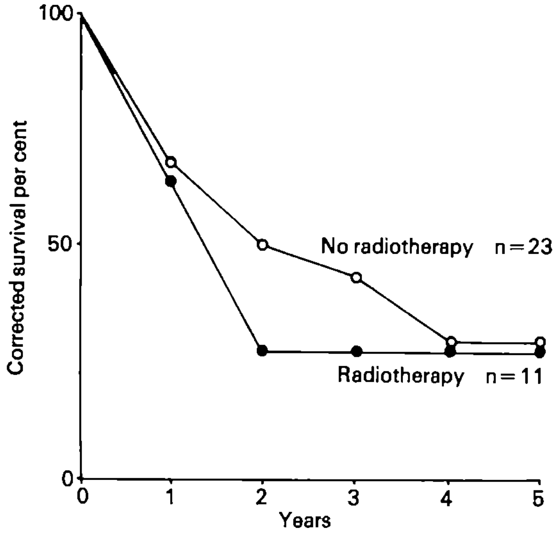

Fig. 6 pT4 tumours and post-operative radiotherapy

Table 8 Ipsilateral Urothelial Recurrences after Conservative Resection

Site of original tumour	No.	Single recurrences No.	%	No	Multiple recurrences No	%
Pelvis	20	0	0	13	5	38.5
Pelvis+ureter	0	0	0	4	1	25
Upper ureter	3	0	0	2	2	100
Lower ureter	11	1	9	5	4	80
Total	34	1	3	24	12	50

(ii) When a tumour is well differentiated and has not invaded muscle, conservative resection offers as good a chance of survival as total nephroureterectomy.

(iii) The risk of recurrence in the urothelium left behind is 13 in 58 (22.4%). When the original tumour was a solitary one there was a recurrence in only 3%, in contrast to a recurrence rate of 50% in those whose original tumours were multifocal.

(iv) Survival and recurrence of upper tract tumours depend not upon their site, *i.e.* whether the tumours arise in the renal pelvis and upper ureter or in the lower third of the ureter, but upon their original grade and stage, and whether they are single or multifocal. In this we disagree with Zincke and Neves (1984).

Indications for conservative resection

These results show that conservative resection can be recommended for single, well differentiated, non-invasive tumours of the upper tract.

When upper tract tumours are multifocal, about half of the patients are likely to develop new tumours in the remaining upper tract: if a conservative resection is contemplated, very careful follow-up is necessary.

In undifferentiated and deeply invasive tumours the results of conservative surgery are very poor and those of total excision hardly much better. Neither is improved by adjuvant post-operative radiotherapy. Our data, like those of Brookland and Richter (1985), once more reveal the need for effective adjuvant therapy (Blandy, 1982).

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Pelviureteric Obstruction in Children Treated by Retrograde Ureteroplasty

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Summary—Pelviureteric obstruction was treated by dilatation with a Fogarty balloon catheter in 2 children. The catheter was introduced through the cystoscope without any percutaneous procedure, ureteric stents or drainage. Follow-up for 18 months indicated improved drainage and renal function. The merits and demerits of this technique are discussed.

Non-operative transluminal dilatations are often performed using balloon catheters to dilate blood vessels (Gruntzig and Kumpe, 1979), the ureter (Kadir *et al.*, 1982), the oesophagus (Goldthorn *et al.*, 1984), the colon (Ball *et al.*, 1985) and the mitral valve (Al Zaibag *et al.*, 1986). We report a new technique for dilating a stenosed ureter in children.

Case Reports

Case 1. O.H., a boy aged 7 years, presented with retention of urine due to a bladder stone which required removal. Intravenous urography and micturating cystourethrography revealed a small pyelonephritic right kidney with grade I vesicoureteric reflux and a stricture of the pelviureteric junction on the left side. Biochemical and haematological results were normal. The area-corrected creatinine clearance was 98.15 ml/min. Renography with an intravenous bolus of 12 MBq of ^{131}I Hippuran and 185 MBq of ^{99m}Tc DTPA and good hydration with an intravenous drip indicated a poorly functioning right kidney and an obstructed left one. In October 1985, when a 4F Gruntzig catheter could not be introduced, a 3F Fogarty catheter was introduced through an 11F 30 cystoscope up to the pelvis of the kidney; 30% Urografin was used to inflate the balloon. Attempts to keep the inflated balloon at the site of stenosis failed, as it tended to slip either up or down. The stenosed segment was dilated by increasing the volumes in the balloon. The balloon ruptured when 1.2 ml were injected and the contrast was seen to escape distally with ease. The balloon assumed a "parachute" (Fig. 1) and then a "dumb-bell" shape during withdrawal from the pelvis into the ureter. Renography in February 1986 indicated improved clearance of the isotope. In May 1986 a 4F Fogarty catheter could be introduced fairly easily and the balloon with 0.5 ml Urografin was easily negotiated through the stricture, which was dilated up to 1.0 ml. Renography 10 days later indicated further improvement.

Case 2. A.S., aged 6 years, presented with haematuria and an intravenous urogram indicated left hydronephrosis due to pelviureteric junction obstruction. Bio-

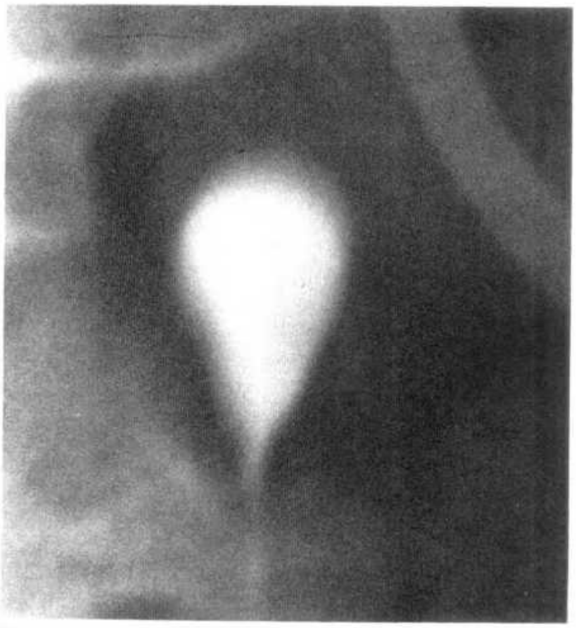

Fig. 1 "Parachute" appearance at the site of pelviureteric stenosis during dilatation while withdrawing the contrast-filled balloon from the pelvis towards the ureter.

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chemical and haematological results were normal. The renogram revealed an obstructed left pelvis. In November 1985 neither a 4F Gruntzig catheter on a guide wire nor a 4F Fogarty catheter could be introduced through an 11F 30 cystoscope, but a 3F Fogarty catheter was successfully positioned. The balloon with 0.1 ml of 30% Urografin was gripped during withdrawal from the pelvis towards the ureter, and by increments of 0.1 ml of air the stenosed segment was dilated to 0.5 ml (Fig. 2), at which point the procedure was stopped. An IVU indicated better filling and better concentration of the contrast when compared with films taken before and 8 weeks after dilatation (Figs 3 and 4). As a "glue effect" had been noticed on an earlier occasion, air was used to inflate the balloon and screening was facilitated because of Urografin in the pelvis. In May 1986 it was possible to introduce a 4F Fogarty catheter and dilatation up to 1.0 ml was effected. The balloon ruptured with a 1.2 ml inflation. The clearance of the isotope improved at 4 weeks and the improvement was maintained at 6 and 17 months. The ultrasonogram at 10 months indicated a reduction in the size of the kidney from 74 to 70 mm.

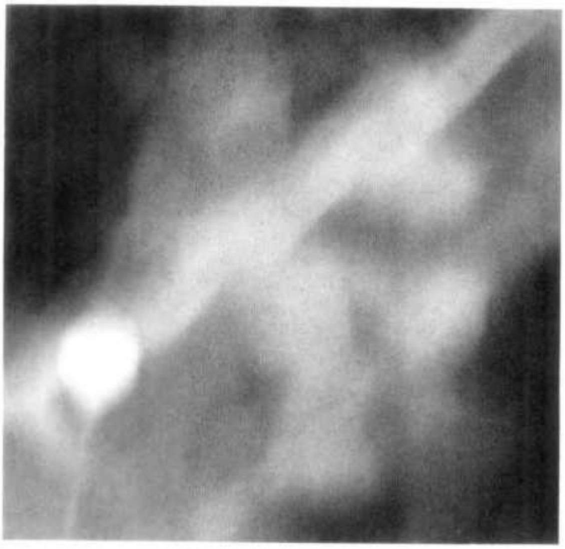

Fig. 2 Urografin in the left pelvis and balloon of the Fogarty catheter with early "parachute" shape during RUBB.

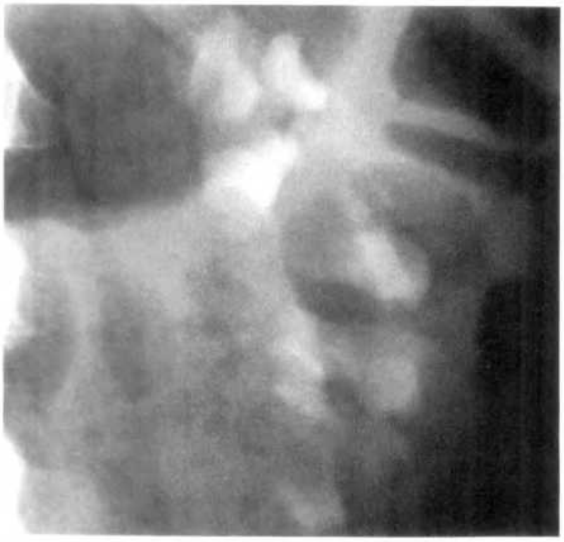

Fig. 3 IVU—5 min before RUBB film—contrast filling the dilated calices.

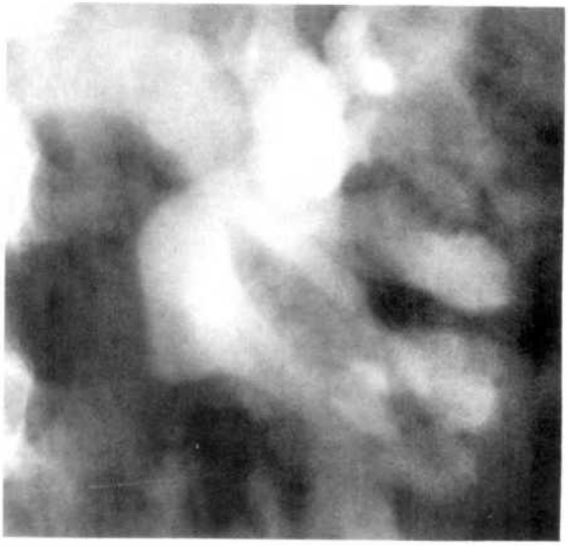

Fig. 4 IVU—5 min after RUBB film—contrast filling all calices and entire pelvis.

Discussion

The first successful retrograde dilatation of a pelviureteric stricture by balloon was performed by Kadir *et al.* (1982) in a 20-year-old woman 6 weeks after a dismembered pyeloplasty which was performed after an unsuccessful attempt to catheterise through the nephrostomy. Ureteric strictures have subsequently been dilated with balloons by percutaneous nephrostomy and/or retrograde catheterisation in adults (Finnerty *et al.*, 1984) and in children (King *et al.*, 1984). All of these authors used the Gruntzig catheter and all of the patients had postoperative strictures. The Fogarty catheter has been used to dilate oesophageal strictures in children (Friedberg, 1979). We believe our report to be the first to describe Fogarty balloon dilatation as a primary procedure for relieving a pelviureteric obstruction.

Since a 4F Gruntzig catheter could not be introduced through the ureteric orifice in either child, a Fogarty balloon catheter was used to negotiate the pelvis of the kidney. Attempts to keep the balloon at the site of the stricture were not successful and it slipped either upwards or downwards during inflation. When Urografin was injected into the balloon a glue-like effect was observed and the balloon could be neither deflated nor inflated. However, the injection of air provided an adequate contrast with Urografin in the pelvis to determine the site and size of the balloon during screening. As the porcedure does not alter the anatomy, failure of retrograde ureteroplasty by balloon (RUBB) should not interfere with any subsequent conventional pyeloplasty procedures.

The technique is simple and safe. Both boys were kept in hospital for 5 days, although we now feel that a 1-day stay would be sufficient following an uncomplicated RUBB. Screening was used during each manipulation, but exposure to radiation can be considerably reduced once the procedure is standardised and more experience is gained.

All previous reports (Kadir *et al.*, 1982; Finnerty *et al.*, 1984; King *et al.*, 1984) have indicated the need for an indwelling tube to remain in the ureter for 1 week to 3 months after dilatation in order to provide drainage and some workers have left the inflated balloon at the site of the stricture for varying lengths of time. This was not necessary in out patients.

The size of the urethra and the currently available balloon catheters prevent the use of RUBB in neonates and infants. However, the success of the procedure in children will encourage its use when suitable equipment and balloon catheters are available.

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Radionuclide Imaging of Ureteric Peristalsis

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Summary—Dynamic renal scintigraphy is a successful and minimally invasive technique for evaluating renal function. An extension to the basic technique involving fast-frame acquisition and a modified analysis is described which enables ureteric function to be examined.

Ureteric peristalsis was assessed in 32 patients using this technique. The results from 5 representative studies are described in detail. Normally functioning ureters exhibit peristaltic contractions at a frequency of up to 3/min. Hyperperistalsis that exceeds 4 contractions/min is associated with obstruction. Peristaltic behaviour in 9 patients examined before and after ESWL was not altered.

The active transport of urine through the ureters is facilitated by peristaltic contractions. These contractions are assumed to initiate from a pacemaker situated in the renal pelvis (Constantinou, 1974). The contribution of functional abnormalities in ureteric peristalsis is rarely considered in urinary tract pathology because methods to examine ureteric function are invasive and therefore of dubious value.

One of the most successful and minimally invasive techniques for examining functional aspects of the urinary tract is the dynamic renal scintigram. This is conventionally performed as a 2-phase, computerised study using fast-frame acquisition of data in the early phase, up to 2 min, to assess renal perfusion, followed by slower acquisition during the clearance of tracer from the kidneys. It has been shown (Muller-Shauenburg, 1985; Sterk *et al.*, personal communication) that by extending fast-frame acquisition to the entire study, ureteric peristalsis may be visualised. This modified scintigraphic technique has been applied in a number of studies involving different renal and urological pathologies to examine its efficacy.

Patients and Methods

The acquisition of scintigraphic data is modified by continuing in the fast-frame collection mode (2 s/frame) throughout the period of study, usually 20 min. Once data acquisition is completed a series of frames from the latter part of the study are summed to determine precisely the position of the ureters. Between 6 and 12 rectangular regions of interest (ROI) are placed over each ureter and background corrected counts from each of the ROIs are then stored as columns of a matrix, one column for each frame of the study (Fig. 1). As a bolus (or spindle) of urine passes through a section of ureter the counts in that ROI will rise above background. In subsequent frames the bolus will have moved further along the ureter and the counts in a different ROI will increase, whilst the counts in the original ROI return to background levels. The variation in activity for each ROI is displayed as a matrix, individual columns of the matrix representing the distribution of activity in the entire ureter during one time frame. The passage of individual boluses of urine down the ureter is indicated by diagonal lines on the display (Fig. 1). Because the matrix has between 6 and 12 rows and approximately 750 columns, it is more convenient to divide it into sections which are displayed one above the next

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Based on a Poster Demonstration at the 43rd Annual Meeting of the British Association of Urological Surgeons in Edinburgh, July 1987

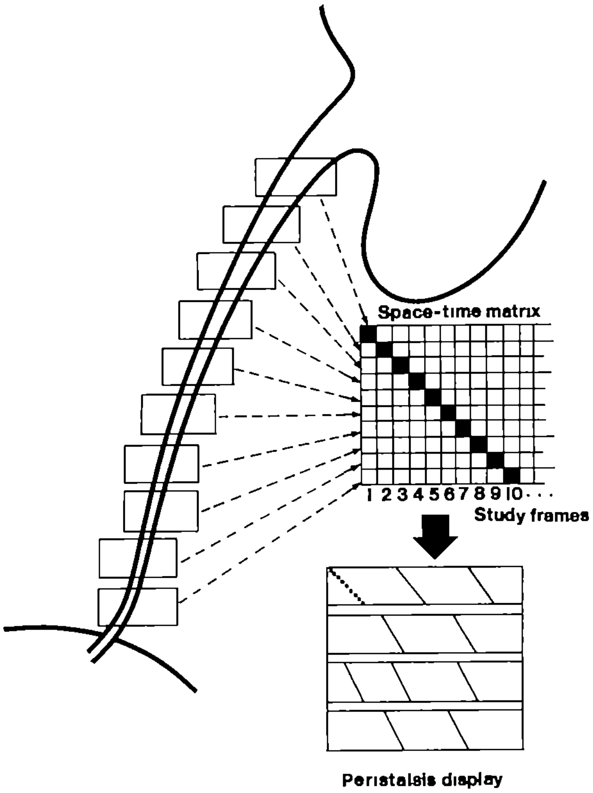

Fig. 1 Creation of peristalsis display

and read like typescript, from top left to bottom right. This forms the "peristalsis display".

To examine the clinical value of this technique, 32 patients with a variety of different pathologies were studied (Table). A series of 5 patients from the study group are discussed below to demonstrate the interpretation of peristaltic displays, which is largely qualitative. Each discussion is illustrated with the corresponding display which also shows the renogram for that kidney and indicates by two vertical bars the region of the renogram over which the peristalsis analysis was performed. The width of the peristalsis display corresponds to a time period of 2 min.

Table

Pathology	*Patients*
Before/after ESWL	9
Ureteric obstruction	7
Reflux	3
Dilated system	3
TUU	2
Ureteric reimplantation	2
Other	6
Total	32

Results

Case Reports

Case 1 A 65-year-old male studied 4 h after ESWL (Fig. 2). The study records the clearance of DTPA from the kidney not subject to ESWL and demonstrates peristalsis at a frequency of between 2 and 3 spindles/min. This is assumed to be normal. Also in this study the peristaltic waves take between 12 and 16 s to pass down a ureter 250 mm in length (measured from an intravenous urogram film), which places the speed of peristaltic waves at between 15 and 20 mm/s. This range of speeds appears relatively unvarying in both normal and abnormal ureters. Towards the end of the study peristaltic waves become less distinct. This is because most of the tracer has cleared from the kidney by this stage.

A total of 9 patients have been studied before and after ESWL for renal calculus. These patients were all treated using a Dornier HM3 lithotripter. No changes in ureteric peristalsis (of either ureter) were observed in any patient.

Case 2. A 44-year-old female with partial obstruction to the lower ureter (Fig. 3) Partial obstruction in this patient is suggested by the relatively slower clearance of tracer indicated by the renogram The accompanying display demonstrates an increased rate of peristalsis at a frequency of approximately 5 spindles/min. It also shows an abrupt termination of peristalsis at the site of obstruction. Hyperperistalsis (>4 spindles/min) is thought to be present in cases of obstruction and could indicate that the peristaltic pacemaker is pressure-sensitive.

Case 3 A 21-year-old male with megaureter (Fig. 4). The renogram in this study indicates poor clearance despite the presence of hyperperistalsis. The most convincing interpretation of this study is that the megaureter constitutes a functional obstruction to clearance and that peristalsis in this type of ureter has a negligible effect on urine flow

Case 4. A 26-year-old female with a neuropathic bladder and single functioning kidney. Tracer activity in the non-functioning kidney demonstrated in this study (Fig. 5) is the result of reflux from a neuropathic bladder The most interesting feature is the observation that the peristaltic pacemaker remains functional in a kidney which has no function.

Case 5. A 35-year-old female 1 month after TUU (transuretero-ureterostomy). In this study the peristalsis displays from both ureters are shown (Figs 6A and B). Also included is an image of the urinary tract to illustrate the positioning of the ureteric ROIs (Fig. 6C). Hyperperistalsis may be observed in both ureters proximal to the anastomosis with ill-defined peristalsis distally. This is

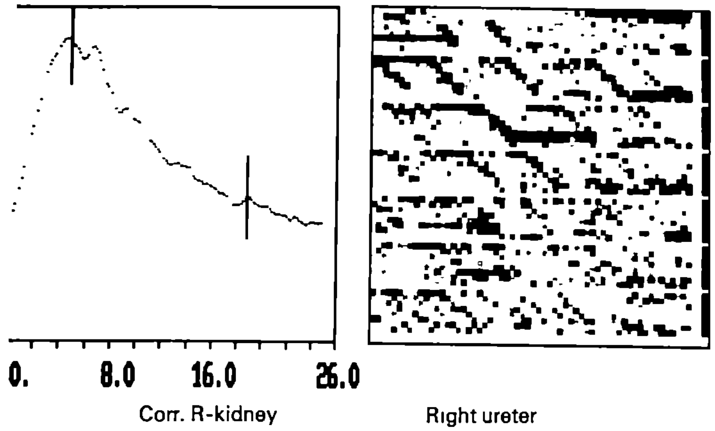

Fig. 2 Normal peristalsis

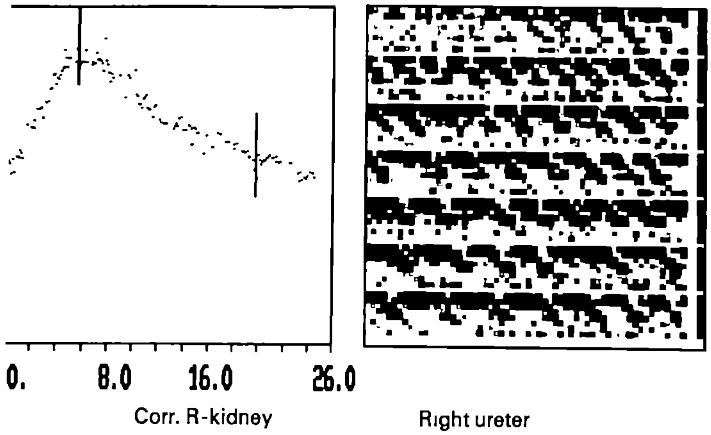

Fig. 3 Peristalsis in obstructed ureter

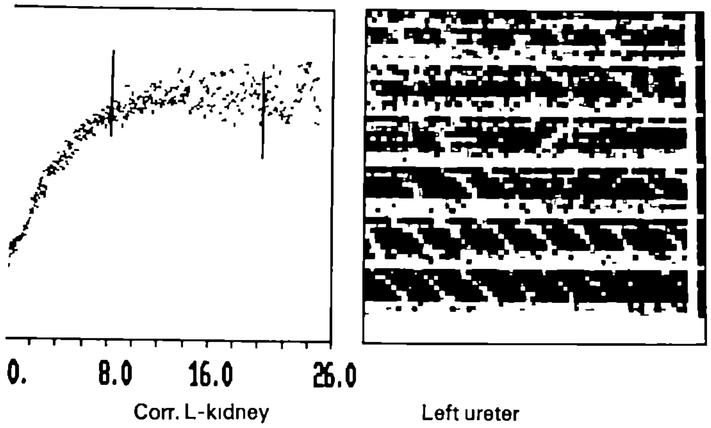

Fig. 4 Peristalsis in megaureter

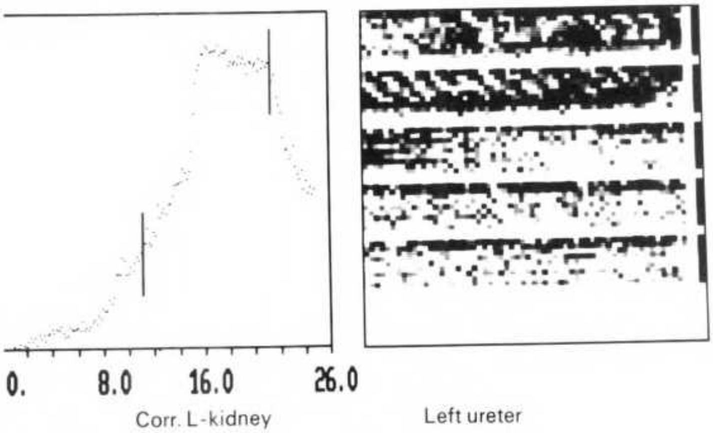

Fig. 5 Peristalsis in ureter from non-functioning kidney.

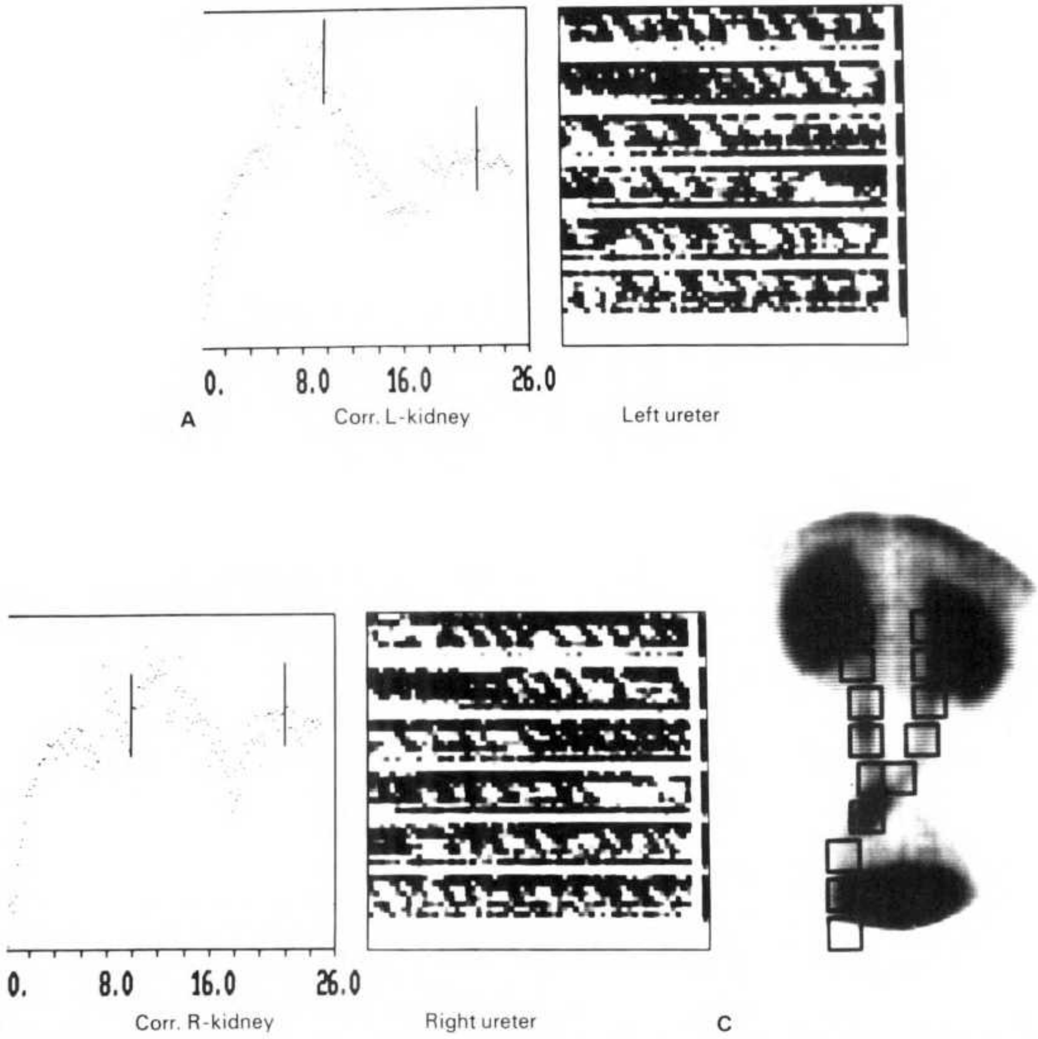

Fig. 6 (A) TUU: peristalsis in left ureter. (B) TUU: peristalsis in right ureter. (C) Positioning of ureteric ROIs over TUU.

assumed to demonstrate obstruction at this site. A further interesting observation is the synchrony of peristalsis in the two ureters proximal to the anastomosis.

Discussion

Experience with this technique indicates that it has the sensitivity to demonstrate ureteric peristalsis. In the 32 patients studied a variety of peristaltic patterns was observed. The most common pathological indicator to emerge was hyperperistalsis in cases of obstruction and this is in agreement with the data presented by Tscholl *et al.* (1976).

One of the most interesting features of the study was the variety of peristaltic behaviour observed. In addition to the distinct patterns of, for example, hyperperistalsis, there were more subtle features, including the length of the individual spindles, their formation and the abrupt changes from one behavioural pattern to another. Clearly these features also contain information which with more experience is likely to be of clinical significance.

The technique is not without problems of both a technical and physiological nature. The need to acquire data at fast-frame rates decreases the signal to noise ratio in the images, thus degrading the quality of the information. This is a particular problem in obese patients and those with poor renal function, although it may be ameliorated to some extent by increasing the tracer dose, from 200 to 300 MBq in the case of ^{99m}Tc-DTPA. The large volume of data collected during fast-frame acquisition increases the time required for processing and the demands on computer storage capacity. Difficulties are sometimes encountered with the state of hydration of the patient. Under conditions of high flow rates the ureters cease peristalsis and behave as simple open tubes. This has been observed in the present study at flow rates between 7 and 10 ml/min (total from both kidneys) and indicates the need to control the patient's fluid intake prior to the study.

A consideration in this work has been the possibility that the patterns observed may be explained as artefacts arising from camera instability or patient motion and amplified by the low signal to noise ratio. In a number of studies in which peristalsis was observed, the data were reanalysed with regions of interest deliberately placed adjacent to but outside the ureters. As expected, the images displayed random noise with no indication of any periodicity.

At this relatively early stage in the evolution of the technique it is not possible to base unequivocal diagnoses on the results of individual studies. However, as more experience is acquired in the interpretation of these studies, it is possible that this technique may be as successful in diagnosing ureteric pathology as the renogram has been in determining renal pathology.

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Transvaginal Ultrasound in the Assessment of Bladder Volumes in Women

Preliminary Report

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Summary—Transvaginal linear array ultrasound is described as a method of measuring bladder volumes in the range 2 to 175 ml, overcoming the limitations of abdominal ultrasound at these smaller (though clinically important) volumes.

The mean error over the range 10 to 175 ml was 23%. Statistical analysis of preliminary data obtained by this technique shows that bladder volume in ml can be calculated by the formula:

$$\text{Volume} = 5.9 \times (\text{height} \times \text{depth}) - 14.6 \text{ ml}$$
$$(95\% \text{ confidence limits} = \pm 37 \text{ ml})$$

Sonocystography by abdominal scanning is recognised as a simple and non-invasive method of assessing residual urine (Hackenberg *et al.*, 1983). However, its clinical usefulness has been limited because it is difficult to visualise small but clinically important volumes (< 150 ml).

We have developed a technique in women using transvaginal linear array ultrasound which gives consistent visualisation in the sagittal plane of bladder volumes from 2 to 175 ml. Larger volumes tend to overfill the limits of the ultrasound screen.

The usefulness of this technique in assessing known bladder volumes has been tested by measuring 2 sagittal bladder diameters.

Patients and Methods

In this preliminary study we used an Aloka Echo Camera (Model SSD—210 DX) employing a 56 mm linear probe (Aloka UST-658-5-5 MHz) designed for transrectal scanning.

The only preparation of the probe was the application of a lubricated condom. The condom was stretched taut over the probe to eliminate any air beneath the condom and fixed by an elastic band. External electronic calipers (Siel Computer ACV-4LS) were used for speed of measurement. These calipers were calibrated against the internal calipers of the Aloka scanner. Measurements were expressed in cm to 1 decimal place.

A series of 23 patients attending a urodynamic clinic were recruited for the study. No fluids were taken by the patients for a period of at least 153 min prior to the study in order to minimise the renal contribution to bladder volume during the study. We recently examined the pattern of diuresis in 20 women following a 1-litre fluid load and found that the bladder filling rate had decreased to 2.5 ml/min or less after 153 min (Haylen *et al.*, 1988).

Each patient emptied her bladder. A size 14 catheter was then inserted to drain any residual urine. A baseline ultrasound examination confirmed that no urine remained visible within the bladder.

Initially, 11 ml of sterile water were instilled into the bladder. This gave a bladder volume of 10 ml after allowing 1 ml for the measured catheter deadspace. A further 15 ml were then inserted to make a total bladder volume of 25 ml. Thereafter, increments of 25 ml were inserted up to a final

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cumulative total of 175 ml. At each volume (*i.e.* 10, 25, 50, *etc.*) the largest bladder image was obtained and measurements were taken of the height (H) and depth (D). "Height" was the maximum bladder dimension in the horizontal axis of the ultrasound screen, representing the supero-inferior sagittal axis. "Depth" was the maximum bladder diameter in the vertical axis of the screen, representing the postero-anterior sagittal axis (Fig. 1).

A total of 166 readings were obtained. No scans were excluded on the basis of suboptimal outline of the bladder contours. Some measurements were restricted by the patient's tolerance of the urethral catheter, though no patient was so discomforted by the ultrasound probe. The mean duration of each series of measurements was 10 min (range 5–16).

Linear regression analysis of the data was performed by the method of least squares, initially comparing the $H \times D$ product with the known filling volume. This process was then inverted statistically to use an $H \times D$ product to predict an unknown bladder volume (Davies, 1961).

Results

Figure 2 shows the regression of the $H \times D$ product on a known volume. The equation for the line of best fit is:

$$H \times D = 2.466 + 0.169 \times \text{known volume}$$

The correlation coefficient is 0.942 ($P < 0.0001$).

If the above data are inverted statistically in order to predict an unknown volume from a known $H \times D$, the equation for the line of best fit becomes:

$$\text{Unknown volume} = 5.9 \times H \times D - 14.6 \text{ ml}$$
$$(95\% \text{ confidence limits} = \pm 37 \text{ ml})$$

The Table shows the mean $H \times D$, standard deviation and coefficient of variation (% error) at each filling volume.

Discussion

Transvaginal ultrasound in the measurement of bladder volumes in women maintains the qualities of safety and simplicity of abdominal ultrasound. It adds the features of clarity of bladder image and accuracy of measurement of sagittal bladder dimensions at lower volumes. All patients in this series tolerated the vaginal probe extremely well, including some women who were post-menopausal and not sexually active.

Hackenberg *et al.* (1983) and Pedersen *et al.* (1975) have suggested that only a qualitative assessment is possible at low bladder volumes, with many false negatives below 50 ml. The study by

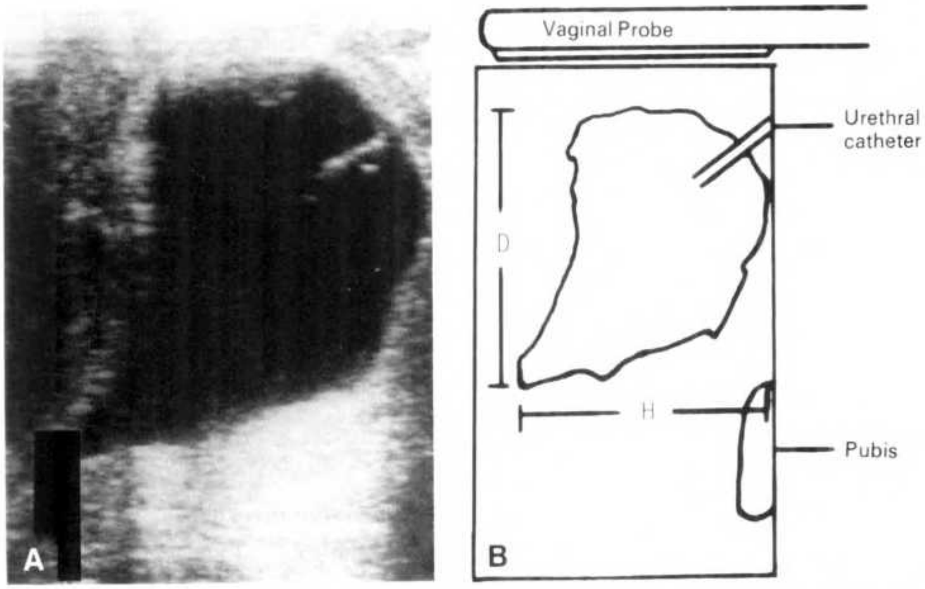

Fig. 1 (A) Polaroid film of typical ultrasonic bladder image in the sagittal plane. (B) Outline of same image to demonstrate orientation and diameters. Bladder height (H) and depth (D) are the maximum diameters in the horizontal and vertical axes of the ultrasound respectively.

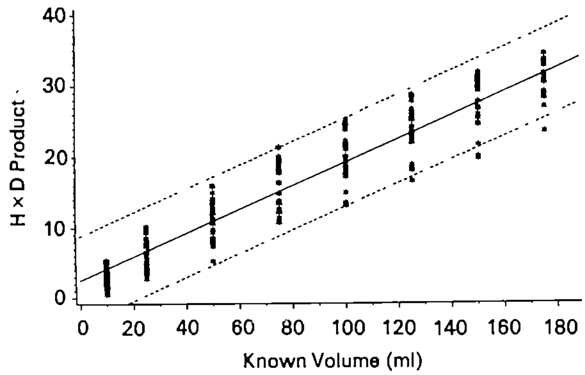

Fig. 2 Regression of the H × D product on a known bladder volume.

Hackenberg *et al.* (1983) is the only one to quote percentage errors for volumes under 100 ml. In the same range of volumes as our series (10–175 ml), their mean percentage error was 94% compared with our 23%. The series of 25 measurements of Ravichandran and Fellows (1983) in volumes below 150 ml was not analysed statistically. Other series involved small numbers of measurements, including those claiming the best results; for example, McLean and Edell (1978) made only 37 measurements after 11 exclusions and Poston *et al.* (1983) made only 17 measurements.

The different shapes and sizes of bladders during filling have been noted by Hackenberg *et al.* (1983) and Kiely *et al.* (1987). Our results represent the "mean relationships", ignoring the differences in shapes and filling between individual women.

The present series involved only diameters in the sagittal plane. Hackenberg *et al.* (1983) highlighted the transverse diameter as the most difficult to measure, reporting similar degrees of accuracy with 2 dimensions in the sagittal plane as with 3 dimensions in 2 planes.

Table Mean H × D Product, Standard Deviation and Coefficient of Variation (% error) at each Filling Volume

Volume (ml)	*Mean H × D*	*SD*	*% error*
10	2.9	1.3	45.7
25	6.3	2.1	33.3
50	11.2	3.0	26.4
75	16.0	3.5	21.9
100	19.8	3.8	19.4
125	23.6	3.5	14.7
150	27.2	3.7	13.7
175	30.4	3.0	9.7

An accurate assessment of the adequacy of bladder emptying in women, as defined by a low residual urine volume, is relevant in many areas of clinical practice, most importantly before and after surgery for urinary incontinence. Using transvaginal ultrasound, a clear assessment is quickly achieved. Further analysis of this technique is being undertaken in order to optimise its quantitative use as well as to assess observer bias and inter-observer differences. We are also investigating its use in other specific areas of clinical practice.

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The Accuracy of Measurement of Residual Urine in Women by Urethral Catheterisation

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Summary—Two potential sources of error in the measurement of residual urine volumes in women were quantified. These were (i) whether a diuresis is operating at the time of measurement, and (ii) the time between voiding and residual urine volume collection.

A regime is suggested for the accurate measurement of residual urine in women by urethral catheterisation.

Residual urine is defined as the volume of fluid remaining in the bladder immediately after the completion of micturition (Bates *et al.*, 1977). It serves as an index of the adequacy of bladder emptying. Its accurate measurement, however, is largely unresearched.

The International Continence Society has stated that two factors of importance when measuring the residual urine volume are (i) whether a diuresis is operating at the time of measurement, and (ii) the time interval between voiding and residual urine collection. If one or both of these are large, then an over-estimation of the residual urine is likely.

In this study we have attempted to set guidelines for the accurate measurement of residual urine by urethral catheterisation.

Patients and Methods

Diuresis factor

A series of 40 women attending a urodynamic clinic were catheterised with a Foley catheter and the bladder was emptied. It was then emptied again 10 and 20 min after catheterisation to assess the baseline bladder filling rate; 20 women then drank 1 litre of fluid (orange juice or water) and 20 women drank 500 ml. The bladder was then emptied at 15-min intervals until the ensuing diuresis had finished, *i.e.* when the bladder filling rate had returned to less than 2.5 ml/min.

The average bladder filling rates over each 15-min period were calculated. By assuming that the rate varies linearly between time intervals, the time at which any set rate is achieved can be estimated by linear interpolation. In this way the times taken for each woman's urine flow rate to slow down after the diuresis to prescribed levels of 10, 7.5, 5, 4, 3 and 2.5 ml/min were estimated.

Time interval between voiding and residual urine volume collection

This was measured in a separate group of 20 women attending a urodynamic clinic. A nurse started a stopwatch immediately the patient ceased to void. A second nurse was scrubbed and ready to catheterise without delay. The timing finished at the end of slow withdrawal of the catheter after the urine flow ceased.

Results

Diuresis factor

The pattern of diuresis in the 20 women subjected to the 1-litre fluid load is shown in Figure 1 and in the 20 women subjected to the 500-ml fluid load in Figure 2.

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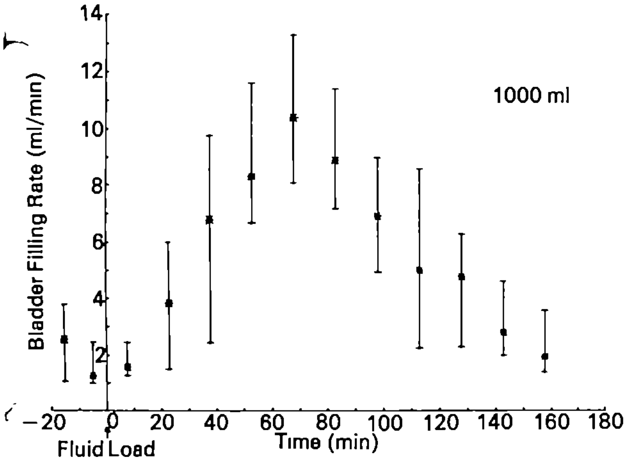

Fig. 1 Bladder filling rates (medians and interquartile ranges) in 20 women before and after a 1000-ml fluid load.

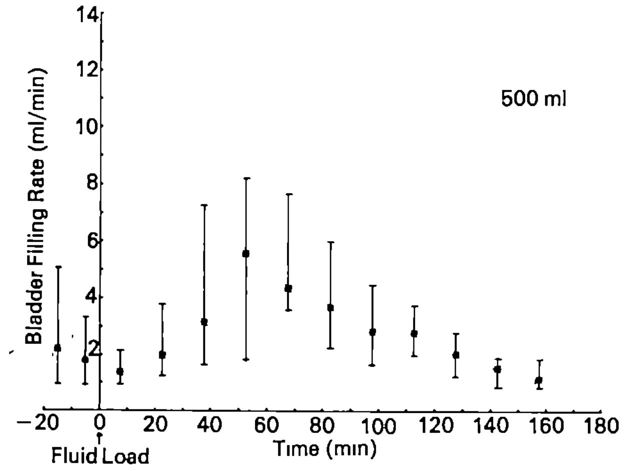

Fig. 2 Bladder filling rates (medians and interquartile ranges) in 20 women before and after a 500-ml fluid load.

The medians and interquartile ranges (25th and 75th centiles) have been used in both Figures because the data set for each fluid load was not normally distributed and at least 100 patients in each group would have been needed to estimate the 95th centile reliably.

The Table shows the times taken (from fluid load) for bladder filling rates in at least 75% of the women to slow down after the diuresis to each of the prescribed rates (10, 7.5, 5, 4, 3 and 2.5 ml/min) for each of the fluid loads (1 litre and 500 ml).

Time interval between voiding and residual urine volume collection

The mean time over 20 measurements was 270 s (4.5 min).

Discussion

The upper limit of normal residual urine volume in women ranges between 50 ml (Bergman and Bhatia, 1985; Lose *et al.*, 1987) and 200 ml (Stanton *et al.*, 1983). The wide variation in these estimates is probably due to inaccurate measurement.

In the second part of the study we tried to create optimal circumstances for rapid catheterisation and for residual urine collection. Even then, the mean time interval between voiding and residual urine collection was 4.5 min. In practice, this could be much longer. The ability to assess the maximum bladder filling rate possible during this period allows an assessment of the accuracy of the residual urine volume measured. Up to 89 min (at which time after a 1-litre fluid load the bladder filling rates of at least 75% of the patients had slowed to 10 ml/min or less), rates of up to 18.3 ml/min are possible. Bladder filling rates of up to 11.0 ml/min are similarly possible up to 42 min in women given a 500-ml fluid load. A significant over-estimation of residual urine with even a 5-min interval between voiding and residual urine collection is possible up to these times.

Our results indicate that residual urine is best measured more than 133 min after a moderate fluid load (500 ml or less) or more than 153 min after a maximal fluid load (500–1000 ml). After these times the bladder filling rate is likely to be less than 2.5 ml/min and potential errors due to the diuresis can be minimised. Residual volumes taken at other times need to be carefully interpreted (Table).

The accuracy of measuring residual urine by urethral catheterisation may be gauged by multiplying the maximal diuretic level at the particular time interval after the fluid load by the time interval between voiding and residual urine estimation. For example, a residual urine volume of 75 ml measured 115 min after a 500-ml fluid load (maximal diuresis 4 ml/min) might be only 43 ml if the delay between

Table Times (from fluid load) when Bladder Filling Rates of at least 75% of the Women Slowed down after the Diuresis to each of the Prescribed Rates

Maximum bladder filling rate (ml/min)	*Time after 1000-ml fluid load (min)*	*Time after 500-ml fluid load (min)*
10	90	51
7.5	118	75
5	132	107
4	138	111
3	150	121
2.5	153	133

voiding and residual collection is 8 min. The maximal over-estimation is then 32 ml.

Once the residual urine is collected, a further potential source of error exists, depending on the device used for measurement. Compared with a 250-ml cylinder (calibration ± 1 ml), we found that the commonly used 500-ml polypropylene jug and the 50-ml syringe gave mean errors of measurement of about 23 and 9% respectively in the range 0 to 100 ml.

Our study has shown that the potential sources of error in the measurement of residual urine by urethral catheterisation can be measured and used to determine whether the presently suggested upper normal limit of residual urine (50 ml) for this parameter (Bergman and Bhatia, 1985; Lose *et al.*, 1987) is correct.

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Are Urodynamics Necessary in Female Patients Presenting with Stress Incontinence?

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Summary—A urological and urodynamic database was used in a prospective study of female patients whose initial symptom was stress incontinence alone. The urodynamic diagnoses in 89 such patients were analysed against any additional symptoms. Fifty-four patients complained of stress incontinence without other symptoms and none of these had detrusor instability. One patient from a group of 25 who had frequency with stress incontinence had low bladder compliance but the others had normal urodynamic studies. Of the 10 patients with urgency in addition to stress incontinence, 5 had unstable bladders.

A detailed urological history must be taken in all patients who are assessed for stress incontinence. Urodynamics are unnecessary in patients with stress incontinence alone but should be considered in those with additional urgency.

The value of urodynamics in the assessment of female patients with stress incontinence is disputed. Jarvis *et al.* (1980) suggested that symptoms were a poor guide to the final urodynamic diagnosis and advocated urodynamic studies in all such cases.

Kaufman (1979) found that the incidence of detrusor instability was low in his patients, including a group which had failed previous surgical treatment for stress incontinence. He concluded that urodynamics were unnecessary in most cases.

A recent study (Byrne *et al.*, 1987) advocated urodynamic studies in all patients with stress incontinence regardless of the history.

Patients and Methods

A detailed history is taken from all patients attending this department for urodynamic assessment, using a standard pro forma. After physical examination the patients undergo multichannel filling (50–100 ml/min) and voiding cystometry with subtracted detrusor pressure. Details from the history, examination and the urodynamic findings are entered prospectively into a urodynamic database. Between September 1985 and October 1987 data were collected in this way on 257 female patients.

The records of those patients whose only reason for referral was the symptom of stress incontinence were analysed (n = 89). Specifically excluded from this study were those patients (n = 123) with urge incontinence and mixed incontinence. From the database records, any additional symptoms were analysed against the urodynamic diagnosis. Patients were considered to have frequency if they consistently voided 8 or more times per day and to have nocturia if they had to get out of bed to void 2 or more times at night. Urgency was defined as a sudden urethral or perineal sensation of precipitant voiding.

The urodynamic tracings of these patients were re-examined and detrusor instability was diagnosed if detrusor contraction occurred or if the intravesical pressure increased by 15 cm of water at any time during the study, using the criteria laid down by the International Continence Society.

Results

The main presenting complaint in all patients was stress incontinence. Urodynamic studies showed 5 of the 89 patients to have detrusor instability (Table). Further analysis on the basis of additional symptoms showed that these 5 patients with instability gave a history of urgency of micturition. Five further patients with urgency had normal

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Table Stress Incontinence (SI), Associated Symptoms and Urodynamic Diagnosis

	SI alone	*SI and frequency*	*SI and urgency*
Stable	54	24	5
Unstable	0	1*	5
Total	54	25	10

*Low bladder compliance

urodynamics; 4 of the 10 patients with urgency also had increased frequency, with over 8 voids per day; 2 of these were shown to have detrusor instability and the other 2 were stable.

All patients with stress incontinence alone without increased frequency or urgency were shown to be stable urodynamically. Stress incontinence with increased frequency was noted in 25 patients. Of these, 17 (68%) also gave a history of nocturia; 1 patient from this group had reduced bladder compliance with a slow, steady rise in pressure to a maximum of 15 cm of water with bladder filling. The studies in the remainder were normal.

Discussion

Genuine stress incontinence of urine is the involuntary loss of urine when the measured intravesical pressure exceeds the measured maximum urethral pressure, but in the absence of detrusor contraction. Most commonly this occurs when the patient coughs or strains. Other conditions may similarly cause incontinence, such as chronic retention of urine and overflow, low bladder compliance and detrusor instability (Staskin *et al.*, 1985). Successful treatment of these conditions depends on accurate diagnosis. In selected cases, genuine stress incontinence is treated by suspensory procedures to the bladder neck. Surgical failure in a proportion of patients has prompted further investigations to define those who would tend to do badly and post-operative persistence of symptoms has been reported in patients with detrusor instability (Bates *et al.*, 1973). It has, therefore, been advocated that all patients should undergo urodynamic studies before surgery, since the histories obtained are poor indicators of the underlying problem.

Patients referred for urodynamics come from a variety of sources, the majority from gynaecologists (82%). The prospective recording of data on a standard pro forma reduces variability between observers and has clear advantages over retrospective studies, where there is a risk of collecting data from poorly detailed urological histories taken by a variety of clinicians.

Byrne *et al.* (1987) reported a 12% incidence of detrusor instability in a retrospective study of 61 patients with stress incontinence unassociated with other symptoms, advocating urodynamic studies in all patients with stress incontinence. However, no details of the completeness of the histories were provided.

Cantor and Bates (1980) analysed urinary symptoms in relation to urodynamic findings and concluded that nocturia, enuresis and urge incontinence suggested instability, but frequency and urgency were unreliable guides to the final diagnosis.

We agree that urodynamics are required in those patients with enuresis and urge incontinence and patients with these symptoms were excluded from this study. Our findings differ from those of Byrne *et al.* (1987) in that all patients with stress incontinence without other symptoms had normal urodynamic studies. In addition, patients with frequency and nocturia were found to have stable bladders.

Detrusor instability was seen in only half of a group of patients who had urgency of micturition in addition to stress incontinence. It was concluded, therefore, that such studies should be performed in patients with urgency, but urodynamics are unnecessary in patients presenting with stress incontinence with or without frequency of micturition. A prerequisite is accurate and complete history taking in the evaluation of these patients.

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Modified Stamey Procedure for Bladder Neck Suspension

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Summary—A review of 76 patients who underwent endoscopic bladder neck suspension (EBNS) for stress incontinence is presented. Pre-operative video-urodynamic studies in 71 patients demonstrated stable stress incontinence in 61 (86%). There was a history of previous pelvic surgery in 52 patients (68%). Surgery was performed by trainee urologists in 35 cases (46%). The overall complication rate was 46%, of which 17% were per-operative and did not influence the outcome of surgery. Infection occurred in 16% and necessitated removal of the suture buffers in 9%. Follow-up ranged from 7 to 30 months (mean 18.3).

Complete resolution of stress incontinence or a marked improvement in symptoms was seen in 86% of cases.

Patients with no history of previous pelvic surgery were all either cured or improved by the procedure. Of the 52 patients who had undergone previous pelvic surgery, 42 (80%) were either cured or improved. All of the 10 failures were in this group. There was no difference between complication or success rates achieved by consultants or urologists in training.

It was concluded that EBNS is the treatment of choice in patients with primary stress incontinence and it is an effective procedure in patients who have undergone previous unsuccessful surgery for stress incontinence.

The first description of a minimally invasive operation designed to cure stress incontinence was by Pereyra in 1959. Stamey (1973) modified this technique and reported on early cases treated by endoscopic bladder neck suspension. In 1980 he reviewed 203 patients and reported a 91% cure rate. This series included a large number of patients who had undergone previous surgery for stress incontinence and 20% were totally incontinent.

Since then there have been many reports of experience with the technique, the cure rates ranging from 40 to 91% (Vordermark *et al.*, 1979; Mundy, 1983; Diaz *et al.*, 1984; Fleischer *et al.*, 1984; Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984; Huland and Bucher, 1984; Fowler, 1986; Affandi *et al.*, 1988). The success rate for EBNS in complicated cases has been examined by some workers who have attempted to establish factors which may adversely influence the outcome of surgery (Arnold *et al.*, 1973; Stamey, 1980; Mundy, 1983; Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984; Affandi *et al.*, 1988). These factors include previous surgery, detrusor instability, chronic cough and "surgically difficult pelvis". Complication rates have differed widely and vary from 15 to 38% (Vordermark *et al.*, 1979; Diaz *et al.*, 1984; Fleischer *et al.*, 1984; Gaum *et al.*, 1984; Huland and Bucher, 1984; Spencer *et al.*, 1987).

In an attempt to assess the success rate of EBNS we reviewed all such procedures over a 2-year period with particular reference to the results in "complicated cases" and those patients in whom surgery had been performed by urologists in training.

Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

Patients and Methods

All patients who had undergone EBNS under the care of two consultant urologists were identified from the operating theatre register and the case notes reviewed.

The surgery performed after clinical assessment and video-urodynamic investigation was as described by Stamey (1973) but with some minor modifications. Prophylactic antibiotics were given. After endoscopic assessment single Stamey needles or a double pronged ligature carrier (Shah, unpublished observations) were passed from the vagina suprapubically (in the majority of cases) using a number 1 nylon ligature and buffers as described by Mundy (1983). After both sutures had been passed, cystoscopy was repeated to confirm that suture placement was correct. A suprapubic catheter was inserted and a vaginal pack left *in situ* for 24 h. The suprapubic catheter was clamped from 3 days post-operatively and removed when satisfactory voiding was achieved with residual urines of less than 50 ml. All patients were reviewed in the out-patient clinic but routine post-operative video-urodynamic studies were not employed.

Results

The notes of 76 patients were available for review. Their ages ranged from 20 to 75 years (mean 49.4). Pre-operative assessment of symptoms suggested that 46 (60.5%) had unstable bladders, 27 (35.5%) were stable and 3 (4%) were known to have neuropathic bladders at presentation. Pre-operative video-urodynamics in 71 patients demonstrated stable stress incontinence in 61 (86%). Acontractile detrusors with stress incontinence were noted in 5 (7%) and only 4 (5.7%) had true instability. A stable bladder but no stress incontinence was noted in 1 patient who underwent surgery with complete subjective success but no change in the post-operative video-urodynamics.

Previous pelvic surgery had been performed in 52 patients (68%) (Table 1).

Dacron buffers were used in 37 patients, PTFE and silicone in 13 patients each, Goretex and Vygon in 6 patients each and Biethium in 1.

Per-operative complications were encountered in 13 patients. In 2, heavy vaginal bleeding was encountered which stopped after local pressure. The suture was passed through the bladder in 11 patients (on both sides in 2). This complication was noted at cystoscopy in all cases, the sutures were repositioned and no long-term problems were encountered.

Table 1 Previous Medical History

No previous pelvic surgery	24
Hysterectomy	13
Pelvic surgery for stress incontinence	
1 operation	11*
2 operations	12
3 "	9
4 "	5
6 "	2
Total	76

* Including 2 previous Stamey procedures

The length of time the catheter remained *in situ* varied from 3 to 165 days (mean 11.5) and the details are summarised in Table 2. One patient with a history of previous cerebral surgery, long-term urethral drainage pre-operatively and an open "stove pipe" urethra continued to leak urine post-operatively despite long-term suprapubic catheterisation. She subsequently underwent urethral closure and this technique would appear to be inappropriate in such cases.

There were 22 post-operative complications. A suprapubic wound haematoma required evacuation in 1 patient and 9 patients complained of some pain and pulling deep to the suprapubic wounds. This symptom resolved by 1 week in 7 patients, by 6 weeks in 1 patient and persisted for 18 months in another patient before spontaneous resolution. The most common complication was infection, noted in 12 cases (16%). The vaginal pack was left in longer than intended in 2 patients. Antibiotics and removal of the pack resulted in complete resolution of pyrexia. One patient who developed a pyrexia for which no cause could be found was treated empirically with antibiotics and the temperature settled. Suprapubic wound tenderness and pyrexia was found in 2 patients and this resolved with antibiotics. Each of these 5 patients had successful results from surgery. Seven patients had a persistent

Table 2 Duration of Post-operative Catheter Drainage

Days	*No of patients*
≤5	22
6–8	40
9–14	9
15–34	4*
165	1
Total	76

* These patients left hospital with a suprapubic catheter and returned for removal when the residual urine fell below 50 ml

discharge and sepsis from either suprapubic or vaginal wounds, necessitating the removal of buffers (Table 3).

Post-operative video-urodynamic studies were performed in 18 patients (24%) (Table 4).

The time spent in hospital ranged from 5 to 22 days (mean 9.2). Out-patient follow-up details were available from 7 to 30 months (mean 18.3).

A complete subjective cure of symptoms was achieved in 52 patients (68%) and a marked improvement in 14 (18%). Of the 5 patients noted to have neuropathic bladders, 2 who were performing self-catheterisation pre-operatively were cured of their incontinence and continued to self-catheterise post-operatively. The remainder were able to void satisfactorily with a combination of abdominal straining and manual pressure. Two patients known to have severe instability pre-operatively were cured of their stress incontinence and subsequently underwent successful augmentation cystoplasty.

There were 10 patients (14%) classified as failures, 8 early (arbitrarily defined as less than 3 months) and 2 late. Of the early failures 5 are scheduled to have repeat EBNS, 1 to have a colposuspension and the 1 patient who subsequently underwent a successful urethral closure. In addition, 1 patient has been successfully treated with a modified Pereyra operation (Raz, 1981).

Table 3 Results in 7 Patients with Persistent Infection Requiring Removal of Buffer

Type of buffer	*1 or both removed*	*Outcome*
Goretex	1	Dry
Goretex	1	Wet
Goretex	2	Dry
Goretex	2	Wet
Teflon	1	Wet
Dacron	1	Wet
Dacron	1	Improved

Of the 2 late failures, 1 patient was initially unable to micturate post-operatively. One suture was loosened and she was able to micturate satisfactorily with no stress incontinence. Four months later, whilst lifting a heavy weight, she felt the loop break and her stress incontinence returned. The other late failure was initially cured but removal of an infected buffer led to a return of stress incontinence.

Two patients had undergone previous unsuccessful Stamey procedures and these were cured by a second operation. There were no failures in the 24 patients who had no history of previous pelvic surgery. Of the 52 patients who had undergone previous pelvic surgery, 35 were cured and 7 improved by EBNS (an overall success rate of 80%). The 10 failures in the series were thus patients who had undergone previous pelvic surgery (Table 5).

Surgery was performed by consultant staff in 41 cases (54%) and the remainder by trainee urologists. There were 28 complicated cases (arbitrarily defined as patients who had undergone between 2 and 6 previous pelvic operations) of which 21 were treated by consultant staff; 18 of the 35 complications and 5 of the 10 operative failures occurred in patients operated on by consultants.

Table 4 Results of Post-operative Video-urodynamic Investigations in 18 Patients

Pre-operative	*Post-operative*	*Subjective*	*Correlation*
Stable SI	Stable SI	Cured	No
Stable SI	Stable SI	Improved	No
Stable SI (× 2)	Stable SI	Failure Repeat Stamey	Yes (× 2)
Stable SI	Stable SI	Failure Colposuspension	Yes
Stable SI (× 9)	Stable No SI	Cured	Yes (× 9)
Stable SI	Stable No SI	Improved	Yes
Stable SI	Unstable SI	Si cured Frequency Urgency	Yes
Atonic SI	Mild instability Mild SI	Improved	No
Atonic SI	Atonic SI	Improved	No

SI = Stress incontinence

Table 5 Results in Patients who had Undergone Previous Pelvic Surgery

Previous operations	*No. of patients*	*Results*		
		Cured	*Improved*	*Failure*
1	24	17	3	4
2	12	9	1	2
3	9	5	1	3
4	5	3	1	1
6	2	1	1	0
Total	52	35	7	10

Discussion

Of the 76 patients in this series, 86% had stable bladders and 68% had undergone previous pelvic surgery, a situation comparable to that found in other large series (Stamey, 1980; Fleischer *et al.*, 1984; Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984; Huland and Bucher, 1984; Fowler, 1986; Affandi *et al.*, 1988).

It is interesting that the patients' history alone suggested that over 60% might have unstable bladders. This was not borne out by the urodynamic findings, which diagnosed instability in less than 6%, and is at variance with the recommendations of some workers who suggest that the diagnosis of instability can be made on history alone (Arnold *et al.*, 1973).

The per-operative complications were minor and similar to those reported by other workers. The passage of a suture or sutures through the bladder is well documented, is easily seen on endoscopy, can be easily remedied and does not give rise to post-operative problems. The incidence should decrease with the experience of the operator. The inclusion of this complication results in an apparently high overall complication rate (35/76 = 46%). If these patients are excluded, the complication rate falls (24/76 = 31.5%) and is comparable to that reported in other series (Vordermark *et al.*, 1979; Diaz *et al.*, 1984; Fleischer *et al.*, 1984; Gaum *et al.*, 1984; Spencer *et al.*, 1987).

The duration of post-operative catheter drainage varied considerably, but the fact that 71 patients (93%) were able to void satisfactorily within 14 days with low residual urines suggests that significant outflow obstruction does not occur (Coptcoat *et al.*, 1987).

Most post-operative problems were minor and resolved rapidly. Post-operative pain or pulling is often described (Diaz *et al.*, 1984; Fleischer *et al.*, 1984) and may be due to nerve entrapment, intrapelvic haematoma formation or just tension in the rectus sheath. If pain is severe or persistent, loosening or division of the suture on that side should resolve the problem.

The avoidance of infection is important and is the complication most likely to necessitate removal of sutures or buffers with subsequent operative failure. Prophylactic antibiotics and the use of inert monofilament sutures should reduce this to a minimum. The implantation of a relatively large foreign material in the form of buffers will obviously increase the risk of persistent sepsis. In addition, Dacron (a woven material) was used in many of the early patients in the series and the use of such material is likely to contribute to a high level of chronic sepsis. In order to reduce this risk we now use small "collars" of PTFE vascular graft. An alternative and cheaper material is a section of silicone nasogastric feeding tube, none of which became infected in this series. The removal of one or more buffers need not necessarily result in failure, with 3 of 7 such cases remaining cured or markedly improved.

The length of time spent in hospital appears high for what is a minimally invasive procedure. It should be possible to discharge patients in the early post-operative period and readmit either as day-cases or overnight for initiation of satisfactory voiding and removal of the suprapubic catheter.

The overall subjective success rate of 86% compares favourably with that of other series. Post-operative video-urodynamic studies were not performed routinely and it may be argued that our subjective successes would not prove so to be with rigorous investigation (Mundy, 1983). Of the 18 patients who underwent post-operative video-urodynamics, good correlation between subjective and objective results was achieved in 14 (12 successes and 2 failures).

Of the 10 failures, 8 were early and were associated with poor patient selection, "complicated" patients and possibly poor technique. Of the 2 late failures, 1 was associated with infection and 1 resulted from a suture breaking after the suture on the other side had been loosened. These findings are in keeping with those of two series which reported the majority of failures as early (Dijkman and Friese, 1984; Fleischer *et al.*, 1984). One report suggested that there was a significant failure rate after 3 months but we did not find this to be the case (English and Fowler, 1988). All of the failures were in patients who had undergone previous pelvic surgery. Such a history is related to a reduced success rate (Arnold *et al.*, 1973; Gaum *et al.*, 1984;

Affandi *et al.*, 1988), but a cure rate of 78% in these patients still confirms the original comment made by Stamey (1973) that this procedure was of value in the "surgically difficult pelvis". The success rate of 100% in primary stress incontinence confirms that EBNS is the treatment of choice in these patients.

There was little difference in the results of patients operated on by senior and those operated on by junior staff and this demonstrates that the operation can be easily taught and learnt. Some critics of the procedure claim that the tightness of the ligature varies widely between patients and between different operators, Despite this, results seem consistently good. We are currently investigating the use of tension spring balancing (Kondo *et al.*, 1987) and transvaginal ultrasound in an attempt to determine the tightness of ligatures sufficient to correct stress incontinence without producing significant outflow tract obstruction.

This study confirms that EBNS is a simple, safe and effective treatment for stress incontinence even in patients with a history of multiple pelvic operations or when surgery is performed by urologists in training. It seems to be particularly successful in patients presenting with stress incontinence and no history of previous pelvic surgery.

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Stamey Needle Suspension for Stress Urinary Incontinence

A Prospective Study of 40 Patients

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Summary—A series of 40 consecutive patients with proven stress urinary incontinence underwent Stamey endoscopic bladder neck suspension. There were 5 cases of detrusor instability and the results were poor in this group. Excluding these patients, 77% were cured and 12% reported significant improvement. There were 4 unpredictable failures; all but 1 occurred within 3 months of surgery and the fourth before 6 months. There were no late failures up to the mean follow-up period of 21 months (range 9–33 months; 35 cases > 12 months); 3 of the failures had the same procedure repeated but it was again unsuccessful. The Stamey procedure is quick, entails minimum high dependency nursing and has a short hospital stay (mean 7 days). As assessed in the medium term, it represents a useful addition to the surgical procedures available for the relief of stress urinary incontinence.

Over a period of 33 months, 40 consecutive patients attending the urological unit with proven stress incontinence who failed to respond to physiotherapy were treated by the Stamey endoscopic bladder neck suspension procedure. The medium-term results of this prospective study are reported.

Patients and Methods

A series of 40 female patients aged between 36 and 75 years (mean 50) were investigated for symptoms of stress incontinence. A routine urological history was taken and all underwent examination (with MSU). Intravenous urography was performed where appropriate (23 cases) and 17 patients also had cystoscopy; 23 patients complained of pure stress incontinence and 17 had stress incontinence associated with frequency and urgency of micturition, occasionally with urge incontinence; 36 patients underwent 4-channel cystometry (Lectromed UIS 5000 apparatus). Urethral pressure profilometry was not performed. Urodynamic studies showed that 31 of 36 patients had stable bladders with no evidence of uninhibited detrusor contractions or a steep pressure rise on medium filling; 5 patients had detrusor instability. In the remaining 4 cases, urodynamic investigation was considered unnecessary; 24 previous anti-incontinence operations had been performed in 15 patients; 8 had had a hysterectomy. The operative recommendations of Stamey (1980) were followed, with 3 minor modifications: 2 small transverse para-urethral incisions were made instead of the single T-shaped incision described by Stamey; superior as well as inferior buttresses were used, using Silastic rather than Dacron; cystoscopy was performed only once following placement of the slings, rather than at each pass of the needle, to determine the mobility and elevation of the bladder neck and to check for bladder perforation. The medial limb of the sling perforated the bladder on one side in 4 cases and on both sides in 1, and required repositioning. At the end of the procedure a 16F suprapubic catheter was placed. It was removed between the fourth and tenth days (mean 6). The hospital stay ranged from 5 to 14 days (mean 7).

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Results

Our definition of "cure" was that suggested by Stamey (1980)—the total absence of post-operative incontinence. Significant improvement was recorded in patients who experienced only rare, minor leakages post-operatively during effort with a full bladder.

The results are shown in Table 1. Of the 40 cases reported, 27 (67.5%) were cured and 4 (10%) were significantly improved; 9 patients (22.5%) remained incontinent; 5 of these had detrusor instability with persisting incontinence of the motor urge variety. If these patients are excluded from analysis, 27 of 35 patients (77%) were cured and 4 (11.5%) were significantly improved; 4 patients (11.5%) without detrusor instability failed. Complications were few and are listed in Table 2. No patient required blood transfusion, no catheter was left *in situ* for more than 10 days and no patient required subsequent sling removal for pain, infection or any other indication. However, 3 patients did have prolonged unilateral pelvic pain requiring non-steroidal anti-inflammatory agents and, in 1 case, ultrasound and local injection of anaesthetic and hydrocortisone; all 3 responded to these measures and had an excellent final result.

Table 1 Results of Stamey Bladder Neck Suspension in 40 Patients

All patients	*No (%)*
Cured	27 (67.5)
Significantly improved	4 (10.0)
Failed	9 (22.5)
Detrusor instability excluded	
Cured	27 (77.0)
Significantly improved	4 (11.5)
Failed	4 (11.5)

Table 2 Complications

	No
Vaginal moniliasis	6
Retropubic pain	3
Wound abscess	2
UTI	2
Haematoma	1
Osteitis pubis	1
Transient retention	1

Discussion

The Stamey endoscopic bladder neck suspension offers certain advantages over other surgical techniques for stress urinary incontinence. It has few contraindications, takes only 25 to 35 min to perform and, in this series, had a success rate in keeping with those reported from other centres (Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984; Green *et al.*, 1986). We did not encounter haemorrhage, deep wound infection, vesicocutaneous fistula or prolonged inability to void, sometimes associated with the need to remove buttresses or slings (Mundy, 1983; Gaum *et al.*, 1984; Green *et al.*, 1986). Such problems can only be attributable to differences in technique and sling tension and the use of Dacron rather than Silastic buttresses. The tying of the slings is a subjective action by the operator but it should be guided by careful endoscopic evaluation of the mobility and position of the bladder neck in relation to the tension exerted on the sling. Extreme tension is never required. It has been suggested that endoscopy of the bladder neck with a forward viewing endoscope by an assistant at the time the sling is tied may help to achieve the optimum position of the bladder neck (Biggers, 1987). The balance between an overtight sling, with subsequent voiding difficulties, and a sling that is too loose, leading to incomplete correction of the incontinence, should thus be minimised.

The success rate for colposuspension by the Marshall–Marchetti–Kranz or the Burch technique is between 74 and 98% (Marshall *et al.*, 1949; Burch, 1961). These are major abdominal procedures with a long hospital stay and several days of high dependency nursing; they may be technically difficult in obese patients or in those who have had previous anti-incontinence or other pelvic surgery. The hospital stay in the Stamey group reported here was 6 to 14 days (mean 7). Even this could be reduced if patients were discharged with the suprapubic catheter *in situ*, to be removed later as a day case. Only 1 day of high dependency nursing per patient was required. The technique was not contraindicated by obesity or previous surgery. Indeed, in the cure group 6 patients had had 2 and 1 patient had had 3 previous failed procedures, while 1 patient had been incontinent for 10 years despite 2 sling procedures, 2 urethral buttress procedures and a colposuspension.

The follow-up in the present series was medium-term, *i.e.* 9 to 33 months (mean 21) (35 cases >12 months). It has been stated that failures following this procedure tend to occur early and certainly within the first 6 months after surgery (Stamey, 1980; Handley Ashken *et al.*, 1984). This is also our experience; 8 of the failures occurred within the first 3 months after surgery and the ninth between 3 and 6 months. To date, no failures have occurred after this time. Longer follow-up will be required for a direct comparison of recurrence rates between this and other procedures.

It has been suggested that the mechanism by which the Stamey procedure restores continence is by the placement of an obstruction at the bladder neck or urethra (Mundy, 1983). This has been the purported explanation for post-operative voiding problems and has been incriminated as a theoretical potential cause of future chronic retention of urine. While a transient obstructive detrusor reaction to the retropubic elevation of the bladder neck is inevitable, our patients had no change post-operatively in mean or peak urinary flow rates and no significant residual urine volumes. In studies where post-operative video-urodynamics have been performed, lateral views confirmed the bladder neck to be elevated behind the pubis, *i.e.* replaced in its anatomically correct position but with no sharp angulation of the proximal urethra. No statistical differences have been noted in urethral length, maximum urethral closing pressure, maximum detrusor pressure during voiding, peak flow rates or urethral resistance after a successful procedure (Leach *et al.*, 1987). Continence in the female is maintained as a result of complex factors involving the pelvic floor, bladder neck and urethra, neurogenic influences on smooth and striated muscle, and abdominal and pelvic pressure transmission characteristics on the proximal urethra and bladder neck. The need for the proximal urethral pressure to exceed bladder pressure during stress elevations in intra-abdominal pressure is a vital component of urinary control. The retropubic elevation of the bladder neck and proximal urethra, and the sling-mediated support for the bladder neck during contraction of the rectus abdominis muscle, are integral features of a successful Stamey procedure.

A rational clinical approach to the management of urinary incontinence in the female is important for successful treatment. We believe that our results support the use of urodynamics to exclude detrusor instability in cases of mixed incontinence in order to avoid disappointing results from inappropriate surgery. In such cases pre-operative treatment of the detrusor instability is advisable if patients are to be rendered dry. Urodynamics will also identify those few patients who are stable pre-operatively but who are rendered unstable by an operative procedure. In this unit, patients without detrusor instability who have genuine stress incontinence and a severe degree of vaginal prolapse are referred for gynaecological opinion. If the prolapse is only mild to moderate, or in cases where there is no prolapse, a trial of intensive physiotherapy is recommended in the first instance. If this fails and stress incontinence persists, urological surgery is performed. The results presented here of the medium-term outcome of 40 consecutive patients undergoing Stamey bladder neck suspension indicate that this is a useful addition to the range of surgical procedures available for the treatment of female stress incontinence. Given its low morbidity, short hospital stay and comparable success rate with other more major procedures, it can be considered a first-line option for surgical treatment, although occasional unpredictable failures must be expected. Although the numbers are small, our experience suggests that such failures should proceed to an alternative procedure, such as colposuspension, rather than a repeat Stamey procedure.

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Metabolic Complications of Cystoplasty

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Summary—A series of 48 patients with intestinal segments incorporated into the urinary tract underwent assessment of acid-base and electrolyte balance. All patients had abnormal blood gas analyses, usually a metabolic acidosis with respiratory compensation; 33% had hyperchloraemia. Radioisotope studies using sodium, potassium and bromine showed that all were absorbed and that absorption was unaffected by renal function.

The results suggest that all such patients, but particularly women and children, may be at risk of the secondary effects of chronic acidosis, especially skeletal demineralisation, unless some compensatory mechanism is working to offset the effects of the acidosis.

Hyperchloraemic acidosis has been recognised as a complication of ureterosigmoidostomy since it was described by Ferris and Odel (1949). A few cases of acidosis have been reported in patients with ileal conduits (Schmidt *et al.*, 1973), rectal bladders (Kerr *et al.*, 1962) and colocystoplasties (Kass and Koff, 1983) which have generally been attributed to pre-existing impairment of renal function.

Whitmore and Gittes (1983), reporting 15 years' experience with caecal and ileocaecal cystoplasty, noted that 6 of 32 patients developed hyperchloraemic acidosis; all of these patients had previously had impaired renal function. Others have found no electrolyte abnormalities in association with these procedures (George *et al.*, 1978; Chan *et al.*, 1980; Light and Engelman, 1986).

There has been no detailed investigation of the electrolyte status of patients with augmentation and substitution cystoplasty and this study was initiated to investigate this question and to quantify the electrolyte absorption across the various intestinal segments incorporated into the lower urinary tract in various ways.

Patients and Methods

The series included 48 patients (age range 9–70 years) who had undergone ileaocaecal segment substitition cystoplasty, ileal or colonic segment augmentation cystoplasty, or ileal conduit urinary diversion (Table 1) at times ranging from 2 weeks to 12 years following their operation.

In the absorption studies the tests were also carried out on 9 patients with an intact lower urinary tract who acted as normal controls.

Electrolyte status was assessed by routine estimations of serum electrolytes, including chloride, on samples of venous blood. Acid-base balance was assessed by arterial blood gas analysis.

Renal function was assessed using Cr-EDTA to measure the glomerular filtration rate (GFR). This was performed separately from the absorption studies to eliminate inaccuracy due to spectral overlap during counting.

Electrolyte absorption was investigated using the radio isotopes sodium-22, potassium-43 and bromine-77 in various combinations. The bromine-77 was used in place of chlorine as the available chlorine isotopes have half-lives of 37 min and 12.5 years, making them impracticable. Bromine has

Table 1 Patients

Substitution ileocaecocystoplasty	18
Colon augmentation cystoplasty	3
Ileal augmentation cystoplasty	19
Ileal conduit urinary diversion	8
Total	48

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Table 2 Isotope Absorption Studies

Patient group	*Br-77*	*Br-77+Na-22*	*Na-22*	*Br-77+K-43*	*K-43*	*Total*
Substitution ileocaecocystoplasty	3	5	4	4	2	18
Colon augmentation cystoplasty	1	1	1			3
Ileal augmentation cystoplasty	4	4	4	6	1	19
Ileal conduit urinary diversion	2	2	2	2		8
Controls	2	2	2	2	2	10

been shown to be a satisfactory substitute for chlorine (Reid *et al.*, 1956).

In each patient an intravenous dose of the isotope(s) was given at time zero and serum samples were taken at timed intervals over the following 24 h. At approximately 24 h a larger dose of the same isotope(s) was instilled into the bladder by means of a 10F catheter. The catheter was then withdrawn. The patients were requested to void exactly 1 h prior to instillation of the isotope and not thereafter, so that the bladder contained some urine at the time of instillation. The urine/isotope mix was held for 1 h, during which time serum samples were taken and the bladder was then emptied. Further serum samples were taken over the following 16 to 24 h.

The samples were separated by centrifugation and 1.5 ml of serum were removed for counting in an LKV 80,000 Gamma counter. One or two of the isotopes were used per patient (Table 2). It was not possible to give all three together as the overlap of their spectra meant that the results would be inaccurate.

Counts were corrected for decay and crossover (Veall and Vetter, 1958) and the fully corrected values, expressed as a percentage of the administered dose per litre, were used to calculate the absorption.

Results

Of the 48 patients in the study, 16 had hyperchloraemia, an incidence of 33%. The incidence was highest in the ileocaecal substitution group (50%) (Table 3).

All of the patients studied were found to have abnormal blood gases. The majority had a metabolic acidosis with respiratory compensation. (Figs 1 and 2).

The isotope studies in controls showed that there was no net absorption of sodium, potassium or bromine from the intact bladder (Fig. 3). In the other groups all patients absorbed the isotopes to some degree. Figure 4 illustrates plots of the corrected counts against time in a typical patient. The rise above the baseline level after intravesical instillation clearly shows that the isotopes have been absorbed.

Table 3 Incidence of Hyperchloraemia

	No	*%*
Ileocaecal substitution cystoplasty	9	50
Ileal augmentation cystoplasty	5	26
Ileal conduit	1	12.5

The levels of absorption appear to vary according to the type of procedure performed, being generally higher in those patients with an ileocaecal substitution cystoplasty than in the other groups (Table 4).

When the rates of absorption were plotted against the time since operation there was no obvious change in the substitution ileocaecocystoplasty group. In the two groups of patients with ileal segment transfers (ileal augmentation cystoplasties and ileal conduit diversions), there appeared to be a reduction in the level of absorption when the early post-operative studies were compared with those conducted later (Figs 5, 6 and 7).

There was no apparent relationship between the level of electrolyte absorption and the patients' renal function (Figs 8, 9 and 10).

Discussion

These results show that electrolyte absorption causing detectable electrolyte imbalance occurs in all patients who have undergone reconstruction of the lower urinary tract using intestinal segments. The level of absorption is not influenced by the level of renal function and there is no change in the absorption across the caecal segments with time since surgery, although there does appear to be a reduction in the percentage of electrolyte absorbed across the ileal segments with time, which may correlate with the development of villous atrophy in the ileal segments. Villous atrophy is well

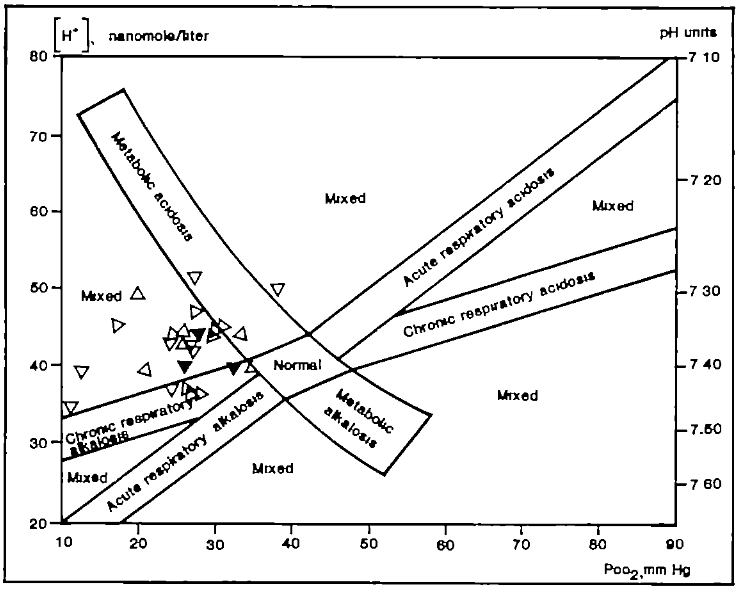

Fig. 1 Results of blood gas analyses—ileocaecal segments and colon augmentation cystoplasties (Levesque, 1975) △ Caecocystoplasty, ▼ Colon augmentation

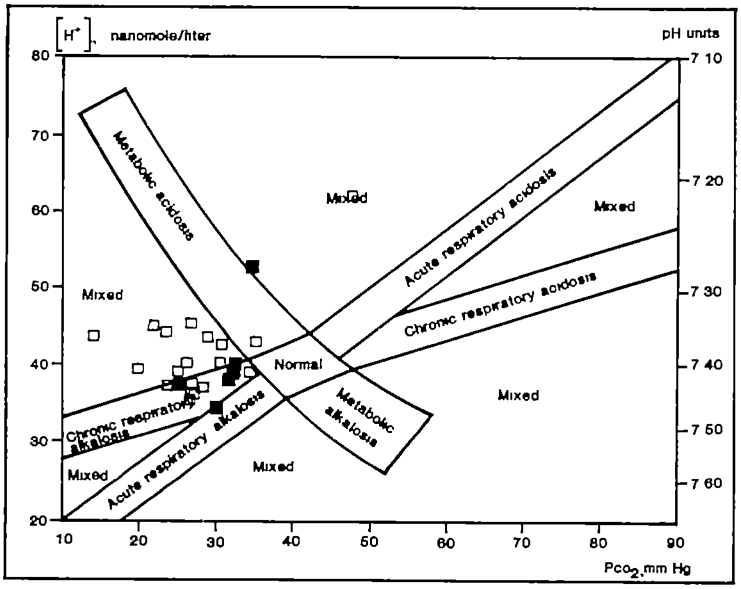

Fig. 2 Results of blood gas analyses—ileal augmentation cystoplasties and ileal conduit diversions (Levesque, 1975). □ Ileal augmentation, ■ Ileal conduit

recognised in ileal conduits, and biopsy studies confirmed some degree of villous atrophy in all of our patients (Nurse and Mundy, unpublished observations).

Thus these results suggest that all such patients are potentially at risk from severe metabolic illness. Similar results have been reported by Caprilli *et al.* (1986). Chronic acidosis is known to be associated with reabsorption of bone, the calcium being lost in the urine. The first description of disordered

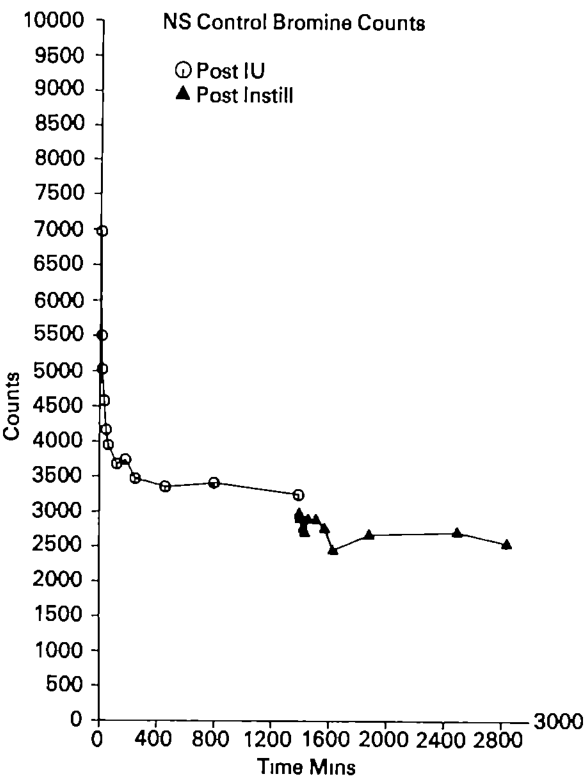

Fig. 3 Isotope study of the intact bladder showing no (bromine) absorption

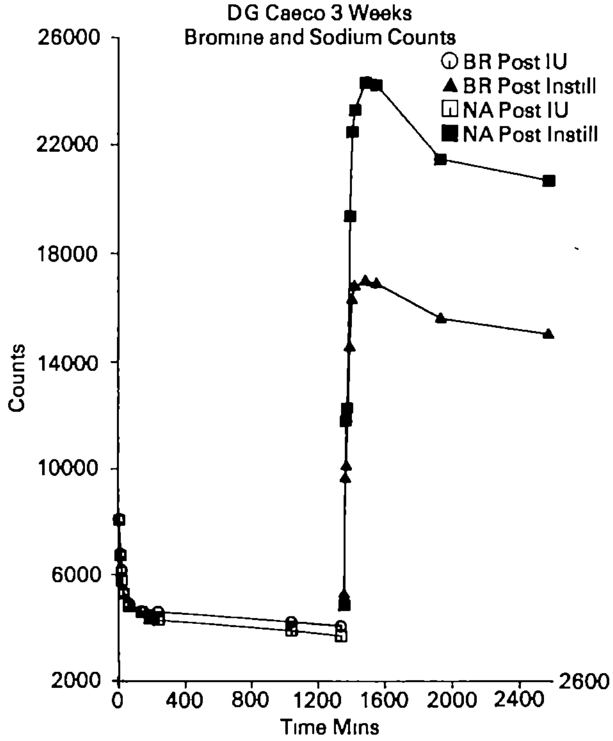

Fig. 4 Isotope study of a patient with ileocaecal segment substitution cystoplasty showing absorption of sodium and bromine.

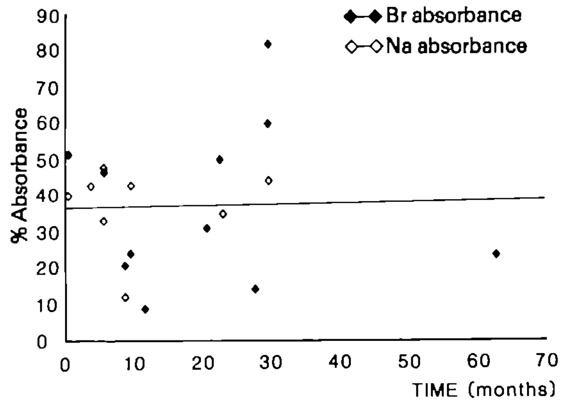

Fig. 5 Electrolyte absorption across ileocaecal segments plotted against months following surgery

bone metabolism occurring in association with ureterosigmoidostomy was made by Boyd (1931), who reported a 10-year-old boy with resistant rickets which responded only when his metabolic acidosis was treated with bicarbonate. In experimental acidosis (Lemann *et al.*, 1966), bony calcium is mobilised and lost in the urine, resulting in osteoporosis in the long term. This suggests that these patients are at risk of skeletal demineralisation, although this has not yet been reported. It may be that this has not been recognised because it has not been sought, particularly as it is not a cause of any acute problem. If it does prove to be a problem it is most likely to be so in women (already at risk of osteoporosis) and children, in whom reduced growth may not be apparent, particularly as many have other problems which cloud the issue. The obvious example is the skeletal deformity and lower limb paralysis (making height measurement meaningless if not impossible) in the spina bifida

Table 4 Absorption

Patient group			
Ileocaecal substitution cystoplasty	3.5–82%	12–48%	18.5–87%
Colon augmentation cystoplasty	18%, 39%	3%, 17%	
Ileal augmentation cystoplasty	1.3–13%	2.5–27%	3.2–17.8%
Ileal conduit urinary diversion	3–26.7%	1%, 2.2%, 21%	7.6%, 17%

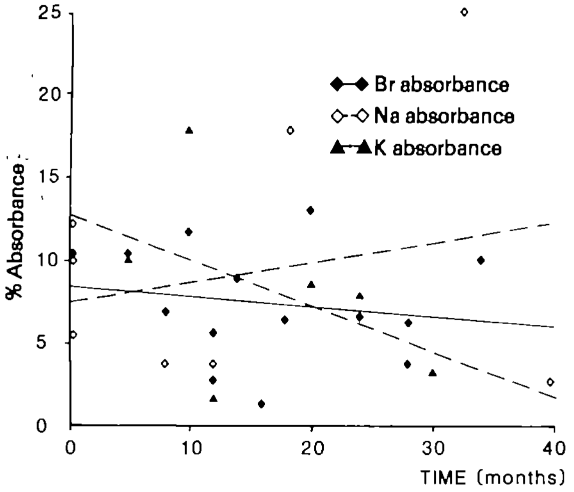

Fig. 6 Electrolyte absorption across the ileal augmentation segment plotted against months following surgery

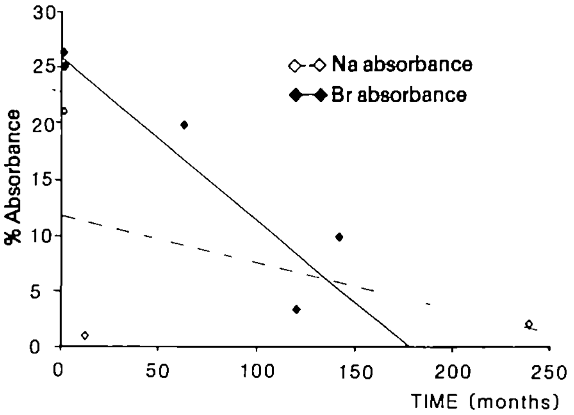

Fig. 7 Electrolyte absorption across the ileal conduit segment plotted against months following surgery.

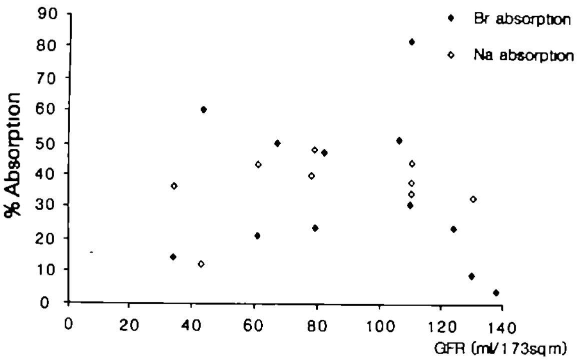

Fig. 8 Electrolyte absorption across ileocaecal segments compared with renal function as measured by glomerular filtration rate (GFR).

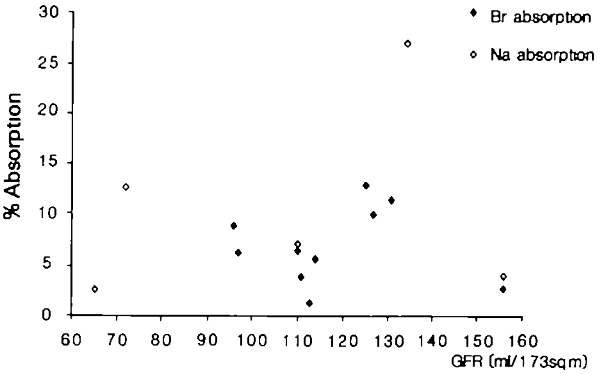

Fig. 9 Electrolyte absorption across ileal augmentation segments compared with renal function as measured by GFR

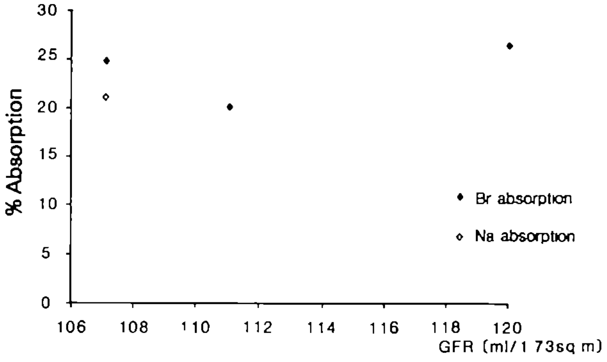

Fig. 10 Electrolyte absorption across the ileal conduit segment compared with renal function as measured by GFR.

children, who are the largest group of youngsters undergoing cystoplasty. This is an area requiring further investigation. It may be that the problems anticipated here are reduced because of reabsorption of calcium from the urine by the intestinal segment, thus keeping the blood levels up and reducing the loss from the skeleton.

The ileocaecal segment seems to absorb a greater percentage of the electrolytes in the urine than the ileal segment, whether used as a cystoplasty or as a conduit. The same group also has a higher incidence of hyperchloraemia, 50% as opposed to 26 and 12.5% respectively. This may be a function of the increased surface area in contact with the urine due to the larger gut segment used in ileocaecal substitution cystoplasty. The fact that histological studies have shown some degree of villous atrophy in all of the ileal segments, and it is the villi where the absorption takes place, may also be relevant. On the question of the degree of absorption, it is interesting that the use of a freely draining conduit appears to confer no advantage over the same segment used as an augmentation cystoplasty.

The question often raised is which type of intestinal segment is the safest. In terms of metabolic balance there is no obvious "best bet", so other factors must be taken into account. One obvious factor in view of the ureterosigmoidostomy experience is that ileum may be better if colonic segments carry a greater risk of long-term malignant change. Further work by Nurse and Mundy (unpublished observations), correlating histological changes, bacteriological studies and N-nitrosamine content of the urine, suggests that all patients with an intestinal segment incorporated into the urinary tract may be at risk in this respect.

This study has shown that when intestinal segments are used in the reconstruction of the lower urinary tract, metabolic acidosis results. It is possible that this will lead to late complications of osteoporosis and stunting of growth and further work is under way to assess this. Since all patients exhibit the same pattern, there is at present no reason to recommend the use of one procedure in preference to others on metabolic grounds. The procedure best suited to the needs of the individual is still the treatment of choice, but all of these patients require close life-long follow-up and prophylactic treatment with sodium bicarbonate may be required.

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Blood Group Antigen Expression in Frozen Sections of Presenting Bladder Cancer: 3-year Prospective Follow-up of Prognostic Value

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Summary—Blood group antigen (BGA) expression was studied on frozen sections from the initial, presenting, transitional cell bladder cancers of 73 patients. Clinical follow-up was prospective and, after 3 years, 59 patients were available for assessment. Of 32 tumours that retained substantial BGA (BGA+ and BGA±), 11 progressed. Of 27 tumours with <5% or undetectable BGA expression (BGA−), 14 did not progress.

Of 24 pTa tumours, 17 had substantial BGA expression and 7 were BGA−; 5 patients progressed, 4 substantially BGA positive and 1 BGA−, all to category pT1; 15 tumours were category pT1, 7 substantially BGA positive and 8 BGA−; 7 patients progressed, 1 substantially BGA positive and 6 BGA−, all of whom died from bladder cancer; 20 were pT2 or deeper, 8 substantially BGA positive and 12 BGA−; 12 patients progressed, 6 substantially BGA positive and 6 BGA−, all of whom died from bladder cancer.

Despite improved understanding of the biochemistry and techniques of detection of BGA, these results preclude the use of BGA determination as a guide to prognosis in individual transitional cell carcinoma, whether used alone or in combination with pT category.

Transitional cell carcinoma (TCC) of the bladder is a heterogeneous disease with an unpredictable outcome in individual cases (Prout, 1982). There are characteristics of a particular tumour which, though not specific, are useful in predicting the eventual prognosis. Those most commonly used in clinical practice include differentiation grade, depth of invasion into bladder wall (pT category), multiplicity and size of tumours (UICC, 1978; Lutzeyer *et al.*, 1982; Heney *et al.*, 1983). Other, more sophisticated techniques, such as chromosomal markers (Sandberg, 1977) or electron microscopy (Pauli *et al.*, 1984) have been studied but have not taken the place of pT category or grade. ABO (H) blood group antigens are not only present on red blood cells but also on epithelial cells (including the urothelium) according to erythrocyte blood group. However, expression in non-secretors is weaker or absent (Szulman, 1960, 1962; Thorpe *et al.*, 1983). Several reports have indicated that urothelial malignancy is associated with reduction or loss of expected BGA and some have related the degree of BGA loss in superficial tumours to the eventual development of progression to muscle invasion and death (Decenzo *et al.*, 1975; Catalona, 1981; Stein and Kendall, 1982). Others, however, have been unable to demonstrate any significant relationship between BGA expression and prognosis (Fujita *et al.*, 1981; Nakatsu *et al.*, 1984). This disparity may be due to differences in the techniques used to detect BGA and difficulties in interpretation of what constitutes a positive or negative result.

We undertook to resolve these conflicting reports by carrying out a prospective study of BGA expression in frozen sections of bladder tumours of various pT categories and grades in order to determine the value of BGA loss as a marker of invasiveness or invasive potential. Most previous studies have used formalin-fixed, paraffin-embedded (FFPE) material, since this allowed retrospec-

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tive studies to be performed. We have previously shown (Thorpe *et al.*, 1983), along with others (Szulman, 1960, 1962; Limas and Lange, 1980, 1982), that BGA are reduced or absent in FFPE sections of normal urothelium but that a reliable assessment of BGA may be made using cryostat sections of fresh-frozen tissue. This is presumably because a substantial proportion of BGA in the urothelium are carried on glycolipid backbones which may be variably extracted by the organic solvents used in processing FFPE sections.

Our results of BGA fluorescence in frozen sections of 73 bladder cancers revealed complete loss of the genetically predicted BGA to be approximately twice as common in TCC that had breached the basement membrane (category pT1 or worse) than in those of category pTa, and also twice as common in poorly differentiated as in moderately differentiated TCC. However, there was no obvious antigenic feature that correlated precisely with pT category or grade (Thorpe *et al.*, 1986).

This is the first prospective study to determine whether there are differences in subsequent behaviour between BGA negative and BGA positive tumours, although there are prospective reports of correlation between prognosis and BGA expression in cytology specimens of patients with bladder cancer (Orihuela *et al.*, 1987).

Material and Methods

All 73 bladder cancers were taken by transurethral resection from the initial tumour only of newly presenting patients, 59 of whom had adequate data for assessment at 3 years and were included in this study. There were 45 males and 14 females, age range 35 to 89 years (mean 68); 30 were blood group A (18 secretors, 7 non-secretors and 5 undetermined) and 29 were blood group O(H) (18 secretors, 2 non-secretors and 9 undetermined). The remaining 14 patients included 5 who died within 3 years from documented non-malignant causes without evidence of bladder recurrences up to the time of death. Clinical records were unavailable for a further 9 patients. These 14 cases were excluded from analysis.

"Superficial" TCC was treated by transurethral resection, with (10 cases) or without (29) additional intravesical chemotherapy. Invasive TCC was treated with either endoscopic debulking and systemic chemotherapy or radiotherapy or cystectomy, depending on the consultant in charge of the case.

Tumour tissue was snap-frozen prior to fluorescence staining for the A and O(H) BGA. These techniques have been described previously by Thorpe *et al.* (1986). Bladder muscle was present in 69 of the biopsy specimens, which were all reviewed by one histopathologist sitting continuously to confirm pT category (UICC, 1978) and grade using the criteria of Mostofi (1973).

In the interpretation of staining, tumours with no antigen fluorescence or antigen fluorescence restricted to <5% of the tumour were designated BGA −. TCC with antigen fluorescence throughout the tumour were designated BGA +. Tumours with focal antigen expression (involving >25% of the tumour) were designated BGA ±. BGA + and BGA ± TCC were grouped together as having "substantial" BGA expression. During the 3-year follow-up period, patients had either no recurrences (NR), non-progressive recurrences (NPR; that is recurrences at the same or lesser pT category or grade) or progressed to muscle invasion, metastasis or death from bladder cancer (PR).

Results

Relationships between BGA expression, tumour differentiation and pT category have been reported elsewhere (Thorpe *et al.*, 1986).

Of the patients with adequate follow-up data, 14 were BGA + (8 pTa, 1 pT1 and 5 pT2–pT4 TCC), 18 were BGA ± (9 pTa, 6 pT1 and 3 pT2–pT4 TCC) and 27 were BGA − (7 pTa, 8 pT1 and 12 pT2–pT4 TCC).

Overall, if TCC with substantial BGA retention (that is BGA + and BGA ±) are considered together, 11 of 32 (34%) progressed compared with 13 of 27 (48%) of the BGA − TCC (Table 1). This difference was not significant ($P=0.28$; chi-square test with Yates correction). If TCC with any loss of BGA are considered together (BGA ± and BGA −; 45 cases), 17 (38%) progressed compared

Table 1 Pattern of Recurrence at 3-year Follow-up According to BGA Expression Alone

	No of patients	*NR (%)*	*NPR (%)*	*PR (%)*
BGA +	14	5 (36)	2 (14)	7 (50)
BGA ±	18	7 (39)	7 (39)	4 (22)
Total positive	32	12 (38)	9 (28)	11 (34)
BGA −	27	7 (26)	7 (26)	13 (48)

NR = No recurrence NPR = Non-progressive recurrence. PR = Progressive recurrence BGA + = Positive throughout tumour BGA ± = Focal BGA loss. BGA − = Negative or virtually negative (<5%) throughout with 7 of 14 (50%) BGA+. This was not significant ($P=0.42$; chi-square test with Yates correction). However, a better correlation with resultant behaviour at 3 years was obtained by combining cases with substantial BGA expression than by combining cases with any BGA loss.

Five of the BGA+ (all blood group O) and 1 of the BGA± group of patients (blood group A) had deeply muscle infiltrating TCC which resulted in death from bladder cancer; 5 patients with deeply infiltrating tumours that were BGA− have had no recurrences at 3 years, 3 of these blood group O and 2 blood group A.

Of the 39 "superficial" (24 pTa and 15 pT1) TCC, 24 were BGA+ and BGA±; 19 (79%) did not progress but 5 (21%) did; 15 were BGA−: 8 (53%) did not progress and 7 (47%) progressed (Table 2).

Of the 20 invasive TCC, 6 of the 8 BGA+ and BGA± group progressed compared with 6 of the 12 BGA− TCC (Table 2). All patients with TCC that progressed died of their disease.

Of the 35 patients whose tumour did not progress, 18 were blood group A and 17 blood group O; 22 were secretors, 4 non-secretors and 9 undetermined. Of the 24 patients whose tumours progressed, 12 were blood group A and 12 blood group O; 14 were secretors, 5 non-secretors and 5 undetermined. Relationships between patients' blood group, type of progression and tumour BGA expression are given in Table 3.

Table 2 Pattern of Recurrence at 3-year Follow-up According to BGA Expression and pT Category (n = 59)

	No. of patients	*Non-progressive (%)*	*Progressive (%)*
pTa category			
Total positive	17	13 (77)	4 (23)*
(BGA+	8	6	2)
(BGA±	9	7	2)
BGA−	7	6 (86)	1 (14)*
pT1 category			
Total positive	7	6 (86)	1 (14)†
(BGA+	1	1	0)
(BGA±	6	5	1)
BGA−	8	2 (25)	6 (75)†
pT2–pT4 category			
Total positive	8	2 (25)	6 (75)‡
(BGA+	5	0	5)
(BGA±	3	2	1)
BGA−	12	6 (50)	6 (50)‡

Abbreviations as in Table 1. (Non-progressive includes those with no recurrences)
*to pT1 †to muscle invasion ‡died TCC.

Table 3 Relationship between Type of Recurrence and Degree of BGA Expression According to Patient's Blood Group

	Blood group A			*Blood group O(H)*		
	Total	*(+*	*−)*	*Total*	*(+*	*−)*
pTa						
NR	7	(5	2)	5	(5	0)
NPR	2	(1	1)	5	(2	3)
PR	3	(3	0)	2	(1	1)
pT1						
NR	0			1	(1	0)
NPR	6	(3	3)	1	(1	0)
PR	4	(4	0)	3	(1	2)
PT$_{2-4}$						
NR	2	(2	0)	4	(1	3)
NPR	1	(1	0)	1	(1	0)
PR	5	(1	4)	7	(5	2)

Abbreviations as in Table 1 (+ = BGA+ and BGA±).

Discussion

The first report of altered BGA expression in transitional cell cancer compared with normal urothelium was made by Kay (1957). Cell suspensions were used to study BGA expression. Organic solvents were not used in sample preparation. There was an approximate relationship between increasing loss of BGA expression and extent of tumour spread but this was not sufficiently accurate for clinical use. Also, one metastasis was BGA+. The work of Decenzo *et al.* (1975) was the stimulus for renewed interest in this test with the publication of their results in 22 cases of superficial TCC. In a follow-up of 5 to 14 years, 8 of 9 patients initially BGA− developed invasive recurrences up to 11 years after presentation compared with none of 13 patients whose original TCC was BGA+. This study was retrospective but was notable for the apparently excellent correlation between BGA expression and subsequent tumour behaviour.

Since then, a number of workers have been in agreement that BGA+ "superficial" tumours have a good prognosis (which is expected because, in this respect, they resemble the parent tissue) and BGA− tumours have a poor prognosis (Lange *et al.*, 1978; Young *et al.*, 1979). However, other authors found a poor correlation between BGA expression and prognosis (Nakatsu *et al.*, 1984) and some have stated that BGA expression provides information of no more value than differentiation grade (Askari *et al.*, 1981). Literature reviews have suggested that while most BGA+ TCC had a good prognosis, up to one-third of the BGA− "superficial" tumours may also have a good prognosis (Catalona, 1981; Stein and Kendall, 1982). These findings make the test difficult to apply in routine clinical management because if it was used as a predictor of the need for radical therapy in patients with BGA− tumours, many would receive unnecessary treatment.

BGA are sugar determinants carried on a glycoconjugate backbone which may be either a protein or lipid (Watkins, 1966). Reports from other centres (Szulman, 1960, 1962; Limas and Lange, 1980, 1982) as well as our own (Thorpe *et al.*, 1983) suggest that a substantial proportion of BGA in the urothelium are carried on glycolipids. Almost all of the studies of BGA expression on TCC have been performed retrospectively and necessarily used FFPE sections. These require processing with lipid-extracting solvents which may account, at least in part, for some of the conflicting results of previous studies.

Few workers have studied BGA in invasive TCC but those that have report few BGA+ cases (Emmott *et al.*, 1979; Richie *et al.*, 1980). However, those who have used techniques without lipid-extracting solvents during processing have shown between 20 and 40% of invasive TCC to be BGA positive (Kay and Wallace, 1961; Fujita *et al.*, 1981). Fujita *et al.* (1981) also observed that over half of their patients with BGA positive TCC actually had metastatic disease. These latter findings are more consistent with our own (40% of invasive TCC substantially BGA+) and support the concept that BGA loss may occur when inappropriate techniques that include lipid-extracting solvents are used.

In general, workers who used FFPE material (Catalona, 1981; Stein and Kendall, 1982) achieved a better correlation between BGA expression and eventual prognosis than those who, as in the present work, did not (Kay and Wallace, 1961; Fujita *et al.*, 1981). This could be because in poorly differentiated, invasive tumours, there is either a reduction in the total amount of glycoprotein present, including that normally expressing BGA, and/or the glycoproteins that are present are not glycosylated normally. The remaining BGA determinants are carried on glycolipids and so may be extracted during processing, giving the appearance of negative sections. This explanation could also account for the more marked reduction or absence of BGA expression that has been reported in non-secretors (Thorpe *et al.*, 1983, 1986). In well differentiated tumours, however, BGA are still present on the glycoproteins. It is paradoxical that the use of methods which are designed to preserve the glycolipid carriers of BGA should give a poorer correlation with present methods of staging bladder cancer and with prognosis than traditional methods.

We considered a result positive (BGA+ and BGA±) when approximately 25% or more of the tissue section was shown to express BGA. This was because all sections were either between 25 to 100% positive or had <5% cells positive (the latter designated BGA−). We recognise that such a division between positive and negative sections is purely arbitrary but others have reported similar criteria (D'Elia *et al.*, 1982). Clearly there was considerable heterogeneity in BGA expression between individual cancer cells in identical tumours and each cell may have a different malignant potential. Grouping together tumours that were BGA− and BGA± (*i.e.* that had all lost some BGA) gave a worse correlation with behaviour at 3 years than grouping together tumours that were BGA+ and BGA±. The fact that 5 of the TCC with BGA throughout the tumour were invasive, and that all of these patients died of their tumour, suggested that separating TCC into those that were BGA+ and those that were BGA± would not show any difference in behaviour. This proved to be the case and longer follow-up of these patients is unlikely to provide additional useful information.

It is now well recognised that pTa TCC have a much better prognosis that pT1 TCC (Anderstrom *et al.*, 1980; Abel *et al.*, 1988). Is BGA expression in TCC a better indicator of prognosis when assessed in conjunction with pT category rather than on its own? In the present study, the only indication that BGA expression may be of additional prognostic value was in category pT1. In this small group of patients, 1 of the 7 BGA± patients progressed and died. Longer follow-up may show more patients to have progressed.

Srinivas *et al.* (1986) reported that blood group A patients had lower grade TCC with lower mortality than blood group O patients. In our study, there were approximately equal numbers of blood group A and O(H) patients amongst those whose tumours progressed and those whose tumours did not progress. A slightly higher proportion of non-secretors (5 of 19; 26%) progressed than did not progress (4 of 26; 15%).

In conclusion, a prospective study of BGA expression in TCC of the bladder, using techniques that did not include lipid-extracting solvents during processing, has demonstrated a poor correlation between increasing BGA loss and tumour behaviour; BGA expression was of no value in predicting prognosis for the individual patient. Research into other tumour associated antigens, provided there is an understanding of the basic biochemistry involved when deciding on the most appropriate techniques for their detection, is likely to prove more fruitful than continued investigation of BGA.

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Recurrence of Superficial Bladder Carcinoma after Intravesical Instillation of Mitomycin-C

Comparison of Exposure Times

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Summary—A total of 70 patients were treated with intravesical instillations of Mitomycin-C (MMC) following transurethral resection for superficial bladder carcinoma. In this randomised prospective study the influence of 2 exposure times (0.5 and 1 h) was studied in relation to tumour recurrence, recurrence interval, tumour progression and toxicity. The number of patients with recurrent tumours was significantly lower in the 1-h group. Tumour progression was seen in only 2 patients in each group and all had primary or secondary carcinoma *in situ* of the bladder or prostatic urethra. Fourteen patients were excluded from further evaluation because of side effects. A longer instillation time over a longer period and a lower dose of MMC are recommended.

Transurethral resection (TUR) is the treatment of choice in patients with superficial bladder tumours. Nevertheless, a recurrence rate of 50 to 70% within 2 to 5 years has been reported and progression of grade and/or stage will develop in 20% of these recurrences (Otto *et al.*, 1984).

In patients with carcinoma *in situ* (CIS) an even greater recurrence rate may be expected because CIS precedes, or is associated with, invasive carcinoma in 40% of patients (Utz *et al.*, 1980).

To prevent recurrence, primary or prophylactic treatment with intravesical chemotherapeutic agents has been used in recent years and Mitomycin-C is considered to be one of the most powerful and successful agents (Mishina *et al.*, 1982; Huland and Otto, 1983; Soloway, 1985). There is, however, no consensus on the choice of drug, dosage, exposure time or number of instillations. The aim of this randomised prospective study was to assess the effect of 2 exposure times (0.5 and 1 h) on recurrence rate, recurrence interval, tumour progression and toxicity following intravesical instillation of MMC.

Patients and Methods

The series comprised 70 patients with superficial Ta/T1 and/or CIS transitional cell carcinoma of the bladder. Informed consent was given in all cases. The diagnosis was made from histological evaluation of resected tissue or biopsies according to UICC (1978) criteria. The study included patients with primary or recurrent carcinoma, presenting with either single or multiple tumours. TUR of all visible lesions and multiple random biopsies of mucosal tissue of the bladder and prostatic urethra were carried out. Two weeks later, patients were randomly allocated to receive instillations of MMC for either 0.5 or 1 h. Women were catheterised after each instillation. Men voided spontaneously and any residual urine was catheterised. Eight weekly instillations of MMC (40 mg in 40 ml 0.9% saline solution) were given, followed by 4 monthly instillations. Side effects which could not be tolerated or treated resulted in withdrawal from the study.

Subsequent clinical evaluations (cystoscopy and urinary cytology) were carried out every 3 months. Patients with recurrent tumours or cytological deviation were treated by repeat TUR and/or bladder mapping. Monthly instillations were given for a further 6 months if histological examination showed Ta or T1 tumour.

Patients were excluded from further evaluation under the following conditions:

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Second recurrence of Ta or T1 bladder tumour.
Persistent occurrence of CIS in the bladder or prostatic urethra.
Infiltration of tumour into the detrusor muscle.
Infiltration of tumour into the prostatic stroma or prostatic ducts.
Development of metastases.

Details of patients are given in Table 1.

Results

Of 70 patients entered into the study, 14 (13 male, 1 female) were withdrawn because of severe toxicity. Each group contained 28 patients, the mean follow-up in the 0.5-h group being 15.7 months and in the 1-h group 14.2 months. The groups were comparable in respect of mean age, sex ratio and distribution of primary or recurrent and single or multiple tumours (Table 1). The incidence of grade I and Ta tumours was higher in the 1-h group and the number of patients with T1 tumours and CIS was higher in the 0.5-h group. Nevertheless, both groups were statistically comparable (Table 2) (χ^2 tests, $P > 0.05$). A histologically proven CIS was divided into primary (without preceding or associated papillary tumour) or secondary CIS. Recurrent tumour developed in 10 patients in the 0.5-h group during follow-up (recurrence rate 2.7 in 100 patient months, mean recurrence interval 36.7 months) (Table 3). The presence of CIS seemed to represent an extra risk factor for developing recurrences in comparison to tumour stage and grade (Tables 4 and 5). No progression in grade was noted in these recurrences and in only 2 patients was progression in stage noted. Both developed a T2 tumour (in 1 case from secondary CIS in the bladder and prostatic urethra after 12 months' follow-up and in the other from primary CIS of the bladder after 9 months' follow-up).

In the 1-h group, 4 of 28 patients developed a recurrent tumour during follow-up (recurrence rate 1.0 in 100 patient months; mean recurrence interval 99.4 months). In this group also the presence of CIS seemed to represent an extra risk factor for recurrences in comparison to stage and grade (Tables 4 and 5). There was no progression in grade but progression in stage was found in 2 patients. Both had secondary CIS (in 1 patient also in the prostatic urethra) and developed infiltrating tumours within 3 and 6 months' follow-up.

Table 1 Details of Patients

	0.5-h group	*1-h group*
No. of patients	28	28
Average age (years) (range)	65.5 (44–84)	66.5 (47–86)
Male/female	20/8	19/9
Primary tumour (%)	16 (57)	13 (46)
Recurrent tumour (%)	12 (43)	15 (54)
Single tumour (%)	11 (39)	16 (57)
Multiple tumour (%)	17 (61)	12 (43)
Average follow-up (months)	15.7	14.2

Table 2 Stage and Grade of Ta/T1 and/or CIS Bladder Tumours

	0.5-h group No (%)	*1-h group No (%)*
No. of patients	28	28
Stage		
Ta	11 (39)	19 (68)
T1	5 (18)	1 (4)
Primary CIS	4 (14)	2 (7)
Secondary CIS	8 (29)	6 (21)
Grade		
I	6 (21)	10 (36)
II	7 (25)	7 (25)
III (incl CIS)	15 (54)	11 (39)

A total of 24 patients (34.3%) experienced 31 episodes of toxicity and 14 had to be excluded from further treatment (Table 6A). The larger number of patients with side effects in the 0.5-h group was mainly due to chemocystitis (Table 6B).

Discussion

Mitomycin-C, an alkylating cytostatic drug, was isolated for the first time in 1956 from *Streptomyces caespitosus*. It inhibits DNA synthesis and in high concentration suppresses cellular RNA and protein synthesis. In 1967 Shida described the intravesical use of MMC to reduce the recurrence rate and recurrence interval as well as tumour progression.

Statistical analysis of our data showed a significantly lower number of patients with recurrences in the 1-h group (χ^2 test; $0.01 < P < 0.05$). Recurrence rates per 100 patient months were 2.7 and 0.1 respectively, correlating with a mean recurrence interval of 36.7 and 99.4 months.

A review of the literature reveals a large variation in recurrence percentages (5.3–84.6%), recurrence rates per 100 patient months (0.3–3.0) and recurrence intervals (33.4–268.3 months) (Denovec *et al.*, 1983; Ausfeld *et al.*, 1987). These data are not comparable because of the variations in dosage (10–40 mg MMC), exposure time (1–3 h), frequency of instillation, time between TUR and the start of treatment, and the duration of treatment (Engelmann *et al.*, 1982; Flüchter *et al.*, 1982; Denovec *et*

Table 3 Percentage of Recurrences, Recurrence Interval, Progression and Average Follow-up

	0.5-h group *No (%)*	*1-h group* *No. (%)*
No. of patients	28	28
Follow-up (months)	15.7	14.2
Recurrences (patients)	10 (35.7)	4 (14.3)*
Recurrence (episodes)	12	4
Progression		
grade	0	0
stage	2	2
Recurrence rate/100 patient months	2.7	1.0
Recurrence interval (months)	36.7	99.4

* (χ^2 test, $0.01 < P < 0.05$)

Table 4 Relation between Stage and Number of Recurrences, Recurrence Rate and Average Recurrence Interval

	0.5-h group				*1-h group*			
Stage	*TA*	*T1*	*Primary CIS*	*Secondary CIS*	*TA*	*T1*	*Primary CIS*	*Secondary CIS*
No. of patients	11	5	4	8	19	1	2	6
Recurrence (No.)	4	0	3	5	0	0	1	3
Recurrence rate/100 patient months	2.0	—	9.4	4.5	—	—	3.5	4.2
Mean recurrence interval (months)	49.6	—	10.7	22.3	—	—	28	23.8

Table 5 Relation between Grade and Number of Recurrences, Recurrence Rate and Average Recurrence Interval

	0.5-h group			*1-h group*		
Grade	*I*	*II*	*III (incl. CIS)*	*I*	*II*	*III (incl CIS)*
No of patients	6	7	15	10	7	11
Recurrence (no)	1	3	8	0	0	4
Recurrence rate/100 patient months	0.87	2.3	4.0	—	—	2.7
Mean recurrence interval (months)	115	44.2	25.1	—	—	36.4

Table 6A Episodes of Toxicity in 70 Patients, Separated by Instillation Group

	Total (n=70) *No (%)*	*0.5-h group (n=36)* *No. (%)*	*1-h group (n=34)* *No (%)*
Episodes of toxicity	24 (34)	18 (50)	6 (18)
Exclusion from treatment	14 (20)	8 (22)	6 (18)

Table 6B 31 Episodes of Toxicity in 24 Patients, Separated by Instillation Group

	Total No	*0.5-h group No.*	*1-h group No.*
Chemocystitis	16	13a	3b
General allergy	10	5c	5d
Contact eczema	5	3	2

Treatment stopped in a—3 patients, b—1 patient, c—5 patients, d—5 patients.

al., 1983; Huland and Otto, 1985; Zincke *et al.*, 1985; Flanigan *et al.*, 1986; Ausfeld *et al.*, 1987).

There is also a large variation in patient selection (preceding or associated CIS and differences in tumour stage) (Huland and Otto, 1985; Zincke *et al.*, 1985). According to our data, the presence of preceding and/or associated CIS seems to be a risk factor in relation to tumour recurrence and this confirms the findings of Jakse (1984) and Somerville *et al.* (1985). In our series, only patients with CIS showed tumour progression, but which of these patients will have a better prognosis is not clear (Weinstein *et al.*, 1980).

The number of patients in our series with side effects (34%) was large compared with the 9 to 36% reported by Flüchter *et al.* (1982) and Flanigan *et al.* (1986). Ausfeld *et al.* (1987), however, reported adverse effects in 49% of their patients.

Contact eczema and general allergic reactions were equally divided between both groups. Generalised exanthema could not be explained by systemic absorption of large amounts of MMC (van Helsdingen *et al.*, 1987). The large number of patients with side effects may be due to our dosage of 40 mg/40 ml and to the different interpretation of these symptoms by other investigators.

In order to prevent tumour recurrence and to prolong the recurrence interval, a minimum instillation time of 1 h is recommended for patients with superficial bladder carcinoma. Adverse reactions were lower in this group, but to reduce these side effects still further we advise dosages below 40 mg/40 ml.

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Trial without Catheter following Acute Retention of Urine

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Summary—A total of 60 patients with acute urinary retention were studied to establish whether a trial without a catheter was justified and to identify subgroups of patients most likely to benefit from this practice. The patients were randomly allocated to 3 groups; the catheters were removed either immediately after the bladder was emptied, or 24 or 48 h later; 17 patients urinated satisfactorily after removal of the catheter. Re-establishment of micturition was not associated with the length of history or severity of symptoms of prostatism, with age or the presence of urinary tract infection. The mean retained volume of urine in patients with a satisfactory result was 786 ml and 1069 ml in the failures. Of the 34 patients with retained volumes of less than 900 ml, 15 were successful in re-establishing micturition compared with 2 of 26 of those with retained volumes greater than 900 ml. The time of catheter removal was not important. The 17 successful patients were reviewed 6 months later. None reported further urinary retention; 6 had required prostatectomy for severe symptoms, 6 had minor symptoms and 5 were symptomless. It was concluded that a trial without a catheter is worthwhile, since 11 of 60 patients had not required surgery, but it should be avoided in patients with a residual volume exceeding 900 ml.

Acute retention of urine is a common reason for the emergency admission of male patients to hospital and is usually managed by urethral catheterisation. Patients with a long history suggestive of severe prostatic obstruction may be best treated by early prostatectomy. Such a history is not always present. In some patients with acute retention of urine, micturition can re-start following removal of the catheter—thus avoiding or at least deferring operation. However, following such a "trial without a catheter", many are unable to micturate and require recatheterisation. This causes discomfort, urethral trauma and increases the risk of infection.

A study was performed to determine how often a trial without a catheter is successful, to identify subgroups of patients where it is most likely to be worthwhile and to establish an optimum time for removal of catheters.

Patients and Methods

During a 9-month period, 83 male patients were admitted with acute urinary retention (defined as a sudden, painful cessation of micturition). Those with significant renal impairment (serum creatinine >200 mmol/l) or clot retention were excluded; 60 patients were studied.

After diagnosis, a 16 F Foley catheter was inserted *per urethram*. The bladder was emptied and the volume of residual urine was recorded. A sample of urine was taken immediately for microscopy and culture. Full blood counts were performed and the serum creatinine, urea, electrolytes and acid phosphatase were measured.

Each patient was asked to state the average number of times of nocturnal voiding during the week leading up to the episode of retention. The patients were randomised into 3 groups according to the time of removal of catheters. One group (18 patients) had their catheters removed immediately after emptying. The others had their catheters

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removed 24 and 48 h later (20 and 22 patients respectively).

The trial without catheter was judged to have been successful if the patient was able to re-establish satisfactory micturition; 6 months after discharge, patients in whom the trial without catheter had been successful were interviewed.

Results

The trial without a catheter was successful in 17 of the 60 patients (28.3%); they were discharged from hospital without operation; 43 patients (71.7%) required recatheterisation. Their subsequent management is shown in Table 1.

The mean age, mean duration of symptoms and incidence of urinary infection in the successful patients were not significantly different but the mean retained volume was significantly smaller (Table 2).

Of 18 patients whose catheters were removed immediately the bladder was empty, 5 successfully re-started micturition (27.8%). Of 20 patients whose catheters were removed after 24 h, 4 were successful (20.0%). Of 22 patients whose catheters were removed 48 h later, 8 were successful (36.4%) (Chi square test, $P>0.05$).

The 17 successful patients were interviewed 6 months after discharge from hospital. None reported further urinary retention; 6 (35.3%) had required prostatectomy for severe symptoms, 6 (35.3%) had only minor symptoms not requiring surgery and 5 (29.4%) were completely symptom-free.

Discussion

Surprisingly little is known about the mechanisms of acute retention of urine in the male. Prostatic infarction (Spiro *et al.*, 1974), alpha-adrenergic overactivity (Caine and Perlberg, 1977) and detrusor decompensation (Powell *et al.*, 1980) may be contributory factors. Urodynamic studies have demonstrated that the internal urethral meatus is closed in retention and release of retention results in an increase in profile length (Murray *et al.*, 1984). Although the first attack of acute retention of urine is usually an indication for prostatectomy (Blandy, 1976), up to 23% of these patients may not require surgery (Murray *et al.*, 1984).

This study refutes the common conviction, based on anecdote, that a successful trial without catheter is more likely when there is a short or absent history of prostatism. Although no significant relationship was established between the likelihood of success and the presence of urinary tract infection, a trend was noted.

Instead it has shown that those patients most likely to benefit from a trial without a catheter are those with a low residual volume of urine: 15 of 34 patients (44%) with residual volumes <900 ml were successful compared with 2 of 26 patients (8%) with a residual volume >900 ml (Chi square test, $P<0.01$). Larger volumes of retained urine cause overdistension of the bladder and loss of detrusor tone (Murray *et al.*, 1984). There is known to be a correlation between large residual volumes and impairment of a measurement of the efficiency of detrusor contractile function (Neal *et al.*, 1987). Several studies have demonstrated an association

Table 1 Subsequent Management of 43 Patients Requiring Recatheterisation

	Number
Transurethral prostatectomy	27
Retropubic prostatectomy	10
Hormonal treatment for Ca prostate	3*
Treatment of meningitis	1*
Treatment of constipation	1*
Permanent indwelling catheter	1
Total	43

* Followed by a successful trial without catheter.

Table 2 Details of Patients

	Successful	*Failed*	*Total*
Number	17	43	60
Mean age*			
Years	72.0	76 9	
Range	57–85	53–86	
Hesitancy†	10 (58.8%)	25 (58 1%)	
Nocturia (× 3 or more)†	8 (47 1%)	20 (46.5%)	
Duration of symptoms†			
No previous symptoms	4	12	16
<3 months	6	11	17
3 months–1 year	2	12	14
>1 year	5	8	13
Urinary tract infection on admission‡	5 (29.4%)	4 (9.3%)	9 (15 0%)
Mean retained volume§			
ml	786	1069	
Range	450–1200	700–2000	

* Mann Whitney test, $P>0.05$
† Chi square test, $P>0\ 05$
‡ Chi square test, $P=0.12$
§ Mann Whitney test, $P=0.014$

between poor urinary flow rates and increased residual volume (Abrams and Griffiths, 1979; Drach and Steinbronn, 1986). Prolonged bladder distension may result in ischaemia (Dunn *et al.*, 1974) and axonal degeneration (Sehn, 1976).

Hesitancy is thought to be a "true symptom" of bladder outflow obstruction (Abrams and Feneley, 1978) but in the present study this symptom was not associated with an increased chance of failure following a trial without catheter. Moderate or severe nocturia (more than × 3) was similarly not helpful in determining those patients likely to benefit from a trial without catheter.

The timing of catheter removal was also shown to be unimportant. Similar rates of success occurred in the 3 groups. Since it is known that the incidence of infection increases the longer the patient remains catheterised (Marshall, 1967), we suggest that the catheter should be removed immediately if trial without a catheter is appropriate.

Many patients with previously minor symptoms welcome a trial without a catheter and our results suggest that some are successful in avoiding surgery—at least in the short term. However, if the retained volume of urine exceeds 900 ml, the chances of success are too small to justify this practice.

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Change in Glycoconjugate for the Binding Site of the Lectin *Ulex europeus* 1 following Malignant Transformation of Prostatic Epithelium

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Summary—Immunoperoxidase techniques were used to detect *Ulex europeus* (UEA1) binding sites on benign and malignant prostatic epithelium. Formalin-fixed, paraffin-embedded (FFPE) and cryostat sections were compared. In benign epithelium, less than 10% of cells on FFPE sections but between 50 and 90% of cells on cryostat sections expressed UEA1 binding sites. In malignant epithelium, more than 90% of cells bound UEA1, irrespective of whether FFPE or cryostat sections were used. Lipid solvents are required for FFPE (but not cryostat) processing and may cause glycolipid extraction. Glycoproteins are not affected. These results suggest that the UEA1 binding site is predominantly glycolipid-based in benign prostatic epithelium but, following malignant transformation, becomes predominantly glycoprotein-based.

Carbohydrates are present on the cell surface attached to proteins or lipids (glycoconjugates). Their expression alters during normal differentiation and malignant transformation and these changes may distinguish cancer cells from their normal counterparts (Feizi, 1985; Feizi and Childs, 1985).

Previous studies of carbohydrate changes in malignancy have included the ABO(H) blood group antigens (BGA). In preliminary work on the immunohistochemical localisation of the A and O(H) BGA in the prostate (Abel *et al.*, 1987b) we showed, using the lectin *Ulex europeus* 1 to detect the O(H) antigen, that between 50 and 90% of cells were positive for the O(H) antigen in benign epithelium. UEA1 receptors were also detected in more than 90% of cells in 7 malignant glands and over 50% of cells in an eighth cancer. These results were obtained using cryostat sections.

Previous workers, using UEA1 on formalin-fixed, paraffin-embedded sections to detect the O(H) antigen, could detect activity in only one-third to two-thirds of benign prostates and never in malignant prostates (Gupta *et al.*, 1973; Stein *et al.*, 1981; Ghazizadeh *et al.*, 1983; Walker *et al.*, 1984). None of these reports gave the proportion of positive cells required in an individual gland to qualify for a positive test.

We inferred that the predominant glycoconjugate carrying UEA1 binding sites in the prostate was glycolipid (Abel *et al.*, 1987b). In order to validate this, we used UEA1 to compare binding sites on both cryostat and FFPE-prepared benign and malignant prostatic epithelium.

Patients and Methods

Prostate chips were obtained by transurethral resection from newly presenting patients. There were 16 men with benign prostatic hypertrophy and 16 with carcinoma of the prostate (prior to any treatment). The presence or absence of malignant epithelium was confirmed histologically in all cases.

Each chip was divided into 2 pieces. One half was snap-frozen and UEA1 binding sites detected as previously described (Abel *et al.*, 1987b). The other half was fixed in formalin and paraffin embedded; UEA1 binding sites were detected using a method for detecting lectin binding sites in

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FFPE sections that has been previously described (Abel *et al.*, 1987a).

The clinical T category was assessed and a bone scan performed in all patients with carcinoma (UICC, 1978). Histological grade was assigned using conventional haematoxylin and eosin sections.

Results

The patients were aged between 63 and 88 years (mean 78). In the malignant cases there were 3 grade 1, 7 grade 2 and 6 grade 3 lesions; 5 were category T1/T2 M0 and 11 had extracapsular or M1 disease (UICC, 1978).

In benign epithelium, less than 10% of cells on FFPE sections but between 50 and 90% of cells on cryostat sections expressed UEA1 binding sites. In malignant epithelium, more than 90% of cells bound UEA1, irrespective of whether FFPE or cryostat sections were used (Table).

There was no relationship between UEA1 expression in prostatic epithelium and the patient's blood group or, in malignant cases, to grade or extent of disease. Endothelium was always positive and acted as a positive control.

Discussion

Immunohistochemical studies of carbohydrate binding sites carried on glycoconjugates should always be studied initially on cryostat material (to avoid complications that may occur during tissue processing, such as the extraction of glycolipids by lipid solvents), but the present work has shown that important additional information may be obtained if FFPE material is studied in parallel.

We have confirmed the findings of our preliminary report (Abel *et al.*, 1987b) that the predominant glycoconjugate carrying UEA1 binding sites in benign prostatic epithelium (BPH) is glycolipid. Our present results with FFPE material in BPH (in which <10% of cells were positive in each case) are not directly comparable with those of previous workers in which BGA was detected in one-third to two-thirds of glands (Gupta *et al.*, 1973; Stein *et al.*, 1981; Ghazizadeh *et al.*, 1983; Walker *et al.*, 1984). These workers did not all state criteria for a positive test and they all used the red cell adherence test, which is less reliable and more difficult to reproduce than immunohistochemical techniques, especially for the O(H) antigen (Cooper and D'Elia, 1982). They also failed to state the specificity of their anti-BGA reagents. When studying BGA activity (as well as expression of lectin binding sites), it is essential to know the precise specificity of the reagents used. BGA are carried on both type 1 and type 2 backbones (Watkins, 1980) and previous work has suggested that only reagents directed against type 2 backbones will detect the O(H) antigen in prostatic epithelium (Abel *et al.*, 1987b). UEA1 detects the O(H) antigen only on type 2 backbones (Pereira *et al.*, 1978).

Table Proportion of Cells Staining Positive for *Ulex europeus* 1 Lectin in FFPE and Cryostat Sections of Benign (BPH) and Malignant (CA) Prostate (%)

	BPH	*CA*
FFPE	<10	90
Cryostat	50–90	90

BGA activity has not been detected in prostatic cancer by previous workers (Gupta *et al.*, 1973; Ghazizadeh *et al.*, 1983; Walker *et al.*, 1984). Loss of BGA activity in prostatic cancer could not therefore be used as a prognostic indicator. Our previous study (Abel *et al.*, 1987b) showed that UEA1 binding sites were detected on prostatic cancer cells when cryostat sections were studied; more than 90% of cells were positive for UEA1 in 7 of 9 cases of cancer (and >50% of cells positive in an eighth case). We inferred from this study, using the historical controls (Gupta *et al.*, 1973; Ghazizadeh *et al.*, 1983; Walker *et al.*, 1984), that the O(H) antigen in malignant prostatic epithelium was probably predominantly glycolipid-based, although we had not yet ourselves assessed binding in FFPE sections of prostatic cancer. Our new finding, that UEA1 binding sites were present in >90% of malignant prostatic cells in FFPE material, suggests that the predominant glycoconjugate in malignant cells is a glycoprotein. This is because FFPE material necessarily undergoes processing with lipid solvents, during which time glycolipid glycoconjugates may be extracted. If glycolipid glycoconjugates predominate, reduced or absent expression would be expected in FFPE compared with cryostat material. If glycoprotein glycoconjugates predominate, expression should be similar, irrespective of whether cryostat or FFPE material is used. Similar difficulties with the detection of glycolipid glycoconjugates have been reported in other tissues, such as urothelium (Limas and Lange, 1980, 1982; Thorpe *et al.*, 1983). It is difficult at present to account for our findings with malignant prostate in the face of previous reports (Gupta *et al.*, 1973; Stein *et al.*, 1981; Ghazizadeh *et al.*, 1983; Walker *et al.*, 1984) but it is likely that other factors are involved, such as the reagents used, length of time tissues were immersed in formalin and the age of the sections studied.

Although we did not assess secretor status, non-secretors do not synthesise BGA determinants on backbone glycoproteins (Watkins, 1980). About 20% of the population are non-secretors. Thus it may be estimated that 3 patients could have been non-secretor. Since more than 90% of cells in malignant prostates were positive for UEA1 binding sites, it is possible that BGA determinants in malignant prostate may be synthesised on glycoprotein backbones. An alternative explanation could be the appearance of new, or unmasking of previously masked, UEA1 binding sites, possibly unrelated to the O(H) BGA.

It is interesting that the predominant glycoconjugate carrying UEA1 binding sites should alter during malignant transformation of prostatic epithelium. This is yet another reflection of the changes in biochemical synthesis which may occur in cancerous tissues. Whether this information will be of use in clinical practice is uncertain, however, because no difference between grades and extent of disease in the patients with malignant disease was found. Perhaps longer follow-up will detect patients with different prognoses but this is unlikely as all of the carcinomas had similar staining properties. Nevertheless, this type of work is important because it draws attention to the value of adopting an approach to the detection of carbohydrates in tissue sections that includes a comparison of cryostat and paraffin sections. A thorough understanding of all aspects of tissue processing is required as a prelude to this type of study.

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Patients at High Risk of Cardiovascular Complications in Oestrogen Treatment of Prostatic Cancer

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Summary—The aim of this study was to predict cardiovascular complications in patients with prostatic cancer treated with oestrogen. A randomised prospective study of oestrogen therapy versus orchiectomy was performed. Patients with pre-existing cardiovascular morbidity were excluded (16%). Prior to the initiation of therapy, patients were subjected to exercise stress tests, physiological evaluation of peripheral circulation, blood volume estimation, chest X-ray, blood test, including hormones, lipoproteins, and antithrombin III, and a physical examination and history by a cardiologist. The oestrogen treatment and the orchiectomy group did not differ with regard to these pretreatment variables; 25% of the patients given oestrogen therapy had cardiovascular complications during the initial treatment year compared with none in the orchiectomy group.

Three statistical discriminating techniques were employed and they allowed us to identify 2 strong discriminating variables for cardiovascular complications if oestrogen therapy is instituted in patients with prostatic cancer but without overt clinical cardiovascular disease. These 2 discriminators were luteinising hormone (LH) and ST-segment depression during exercise. This means that a patient with ST-segment depression during an exercise test and/or a high luteinising hormone concentration should not be treated with oestrogen.

Hormonal treatment in the form of oestrogen or surgical castration has been used for more than 4 decades since the beneficial effects in patients with prostatic carcinoma were reported by Huggins and Hodges (1941) and Huggins *et al.* (1941a, b). The Veterans Administration Cooperative Urological Research Group (1967a, b) published their first report which documented excessive mortality from cardiovascular diseases in prostatic carcinoma patients treated with oestrogen. The oestrogen dose in that study was 5 mg diethylstilbestrol/day. An additional study by the same group showed that a dosage of 1 mg diethylstilbestrol/day did not increase cardiovascular morbidity (Bailar *et al.*, 1979). During the same period a combination treatment with intramuscular polyoestradiol phosphate and oral ethinyloestradiol was introduced and was also reported free of cardiovascular effects (Jönsson *et al.*, 1975). However, more recent reports have indicated an increase in cardiovascular morbidity even with the oestrogen dosages used today (Hedlund *et al.*, 1980).

The cardiovascular side effects during oestrogen therapy have included acute myocardial infarction, unstable angina pectoris, cerebrovascular lesions, intermittent claudication, congestive heart failure, deep vein thrombosis and hypertension. Because of increased cardiovascular morbidity during oestrogen therapy and the psychological impact of surgical castration, it is important to try to predict patients at risk of cardiovascular morbidity if oestrogen treatment is started. Apart from being more than 75 years old or having a history of cardiovascular disease, no predictors of oestrogen-associated cardiovascular morbidity have been identified hitherto in patients with prostatic cancer (Byar and Corle, 1977; Hedlund *et al.*, 1980).

We reported earlier that the use of linear discriminant analysis allowed us to predict patients at high risk of developing cardiovascular complications if oestrogen therapy were instituted (Henriksson and Johansson, 1987). We have now

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confirmed these findings by logistic discriminant analysis. Furthermore, the application of the tree regression technique has enabled us to produce a practical flow chart that should be helpful to the clinician in the evaluation of individual patients.

Patients and Methods

A total of 122 consecutive patients aged up to 75 years with recently diagnosed prostatic cancer, suitable for hormonal treatment in the judgement of a senior urologist, were considered for the study. They were recruited between November 1980 and July 1984 in the Department of Urology, Huddinge Hospital; 19 patients (16%) were excluded because of pre-existing cardiovascular morbidity: myocardial infarction, cardiac decompensation, severe angina pectoris, severe intermittent claudication, cerebrovascular lesions or thromboembolic episodes; 3% of the remaining patients refused the cardiovascular examinations. The remaining 100 patients underwent clinical and laboratory investigations prior to randomisation. The patients in the oestrogen treatment group and those in the orchiectomy group showed no significant difference in these pre-treatment variables (Henriksson and Edhag, 1986); 53 were allocated to oestrogen therapy and 47 to orchiectomy. The tumour categories were T1 (3 cases), T2 (24), T3 (40) and T4 (33). The ethical aspects of the study were approved by the Ethics Committee of Huddinge Hospital.

Patients were screened for a history of cardiovascular disease or risk factors for these diseases and subjected to exercise tests in conjunction with physiological evaluation of peripheral circulation and estimates of blood volume and antithrombin III concentrations; they were also given a chest X-ray examination.

Exercise testing

Graded bicycle exercise tests were performed in the upright position using a bicycle ergometer. The workload was increased by 10 watts/min until the subject stopped because of fatigue, central chest pain or dizziness. Coronary insufficiency was estimated as the amplitude in mV of a flat or downward-sloping ST-segment depression from the baseline in leads CH_2 and CH_5 (Sheffield, 1980). Maximal working capacity was expressed in watts.

Physiological evaluation of the peripheral circulation included measurement of the difference between the brachial artery pressure and the toe blood pressure. Blood volume estimations were made with ^{125}I-labelled albumin. Blood pressures were measured with a mercury sphygmomanometer after 10 minutes' rest and expressed as the mean of the right and left arm values. Korotkoff's fifth point was used in the estimation of diastolic blood pressure.

Blood tests

Blood samples was drawn from an antecubital vein without tourniquet after overnight fasting. Blood glucose, cholesterol, HDL cholesterol, triglycerides, cortisol, follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin, testosterone, creatinine, gamma-glutamyl transferase and antithrombin (AT III) were determined by standard routine methods.

Treatment

Oestrogen was given in the form of polyoestradiol phosphate 160 mg i.m. every month for the first 3 months, followed by 80 mg i.m. per month. In addition, the patient received ethinyl oestradiol 1 mg by mouth daily for the first 2 weeks followed by 150 µg daily. Bilateral orchiectomy was performed under general anaesthesia.

Follow-up and end-points

All patients were followed up for 1 year, the last patient completing his follow-up year in August 1985. The end-points of the study were identical with the exclusion criteria listed above, *i.e.* major cardiovascular events comprising myocardial infarction, cardiac decompensation, severe angina pectoris (medically intractable), severe intermittent claudication (indication for reconstructive surgery), cerebrovascular thrombosis or embolism, and thromboembolic episodes.

Statistical methods

Previous linear discriminant analysis showed that a function comprising 4 variables—LH, cholesterol, FSH and ST-segment depression in lead CH_2—correctly classified a maximum number of patients with complications (62%) (Henriksson and Johansson, 1987). This method is rather technical and difficult to apply in clinical work.

A more practical method is tree classification according to Breiman *et al.* (1984). The goal is, given a set of measurements in a case, to find a systematic way of predicting what class it is in. Tree-structured classification is a recursive and iterative procedure that requires the specification of only a few elements, *i.e.* a rule for selecting the best split at any node and a criterion for choosing the right-sized tree. The stepwise tree structure involves an optimisation at each step over a large number of possible splits of the data. To evaluate the results in this study a V-fold cross-validation was used (V = 10). This means that a tree was constructed from a random sample consisting of 90% of the cases and the rest was classified by this tree. The procedure was repeated 10 times.

A stepwise logistic discriminant analysis (Dixon, 1981) was also employed to confirm or refute the obtained predictors from the tree classification and the linear discriminant analysis. The logistic risk function predicts the risk of cardiovascular complication. The results of the logistic discriminant analysis were cross-validated by the "leaving-one-out" procedure (Lachenbruch, 1975).

Results

Cardiovascular events

In the first year of treatment, 13 patients in the oestrogen group suffered major cardiovascular events compared with none in the orchiectomy group ($P = 0.0008$) (Henriksson and Edhag, 1986). The majority (54%) were arterial ischaemic events and 31% were deep vein thrombosis. Congestive heart failure constituted the remaining events. Cardiovascular events in the oestrogen therapy group were myocardial infarction in 3 patients, intractable angina pectoris in 2, cerebral infarction in 1, severe intermittent claudication in 1, congestive heart failure in 2 and deep vein thrombosis in 4.

Linear discriminant analysis

The results of the classification from the linear discriminant function in the previous study are presented in Table 1. The total figure for correctly classified patients was 84%. However, the sensitivity was low (62%) (Table 2). The univariate technique did not allow discrimination between high-risk and low-risk patients (Henriksson and Johansson, 1987).

Tree regression

The classification tree was constructed with the following variables: ST-segment depression in lead CH_5 during maximal exercise, LH, diastolic blood pressure and triglycerides with 2 final risk nodes (Fig.). Compared with the linear discriminant analysis, 2 variables agreed, *i.e.* LH and ST-segment depression during maximal exercise. The cross-validation resulted in 76% correctly classified patients (Table 1). The sensitivity and specificity were the same (Table 2). One of the variables, triglycerides, gave a medically inadequate final risk node and should therefore be deleted.

Logistic analysis

The logistic function derived by a stepwise procedure (Dixon, 1981) included the following variables: ST-segment depression in lead CH_2 during maximal exercise, LH, cholesterol and FSH, with the risk equation $= 1 + \exp(14.9 - 2732.5\ CH_2 + 0.3\ FSH - 0.44\ LH - 1.41\ LDL)^{-1}$. Cross-validation by the "leaving-one-out" method gave a slightly better result, but the sensitivity was lower (69%) than by tree classification. The total figure for correctly classified patients at an optimal cut-off point was 84% (Table 1).

Tree classification gave the highest sensitivity but the total sum of misclassified patients was somewhat higher (Table 2). The methods of cross-validation are not exactly the same in all analyses.

Table 1 Cross-classification of 51 Oestrogen-treated Patients with Respect to Actual and Predicted Complications

Group	*R− (%)*	*R+ (%)*	*Total (%)*
Tree classification (Total correctly classified: 76%)			
C−	29 (57)	9 (18)	38 (75)
C+	3 (6)	10 (19)	13 (25)
Total	32 (63)	19 (37)	51 (100)
Logistic discriminant analysis (Total correctly classified. 84%)			
C−	34 (67)	4 (8)	38 (75)
C+	4 (8)	9 (17)	13 (25)
Total	38 (75)	13 (25)	51 (100)
Linear discriminant analysis (12) (Total correctly classified 84%)			
C−	35 (69)	3 (6)	38 (75)
C+	5 (10)	8 (16)	13 (25)
Total	40 (78)	11 (22)	51 (100)

C+ : with complications. C− : without complications
R+ predicted risk R− . predicted non-risk

Table 2 Sensitivity, specificity and Total Percentage of Correctly Classified Patients with Cross-validated Data from Tree Classification and Logistic and Linear Discriminant Analysis.

Method	*Sensitivity (%)*	*Specificity (%)*	*Total (%)*
Tree classification	77	76	76
Logistic discriminant analysis	69	89	84
Linear discriminant analysis	62	92	84

This means that the classification result of the linear discriminant function is probably too low. Two patients with complications—deep vein thrombosis and myocardial infarction—were misclassified both by the logistic and the linear discriminant functions.

Discussion

We have now further confirmed our findings from the linear discriminant analysis. The logistic regression technique yielded the same 4 discriminating variables, LH, FSH, cholesterol and coronary insufficiency, as in the linear discriminant function. The tree classification yielded 3 discriminating variables: coronary insufficiency, LH and diastolic blood pressure. This means that 2 discriminating variables are common to all 3 techniques: LH and coronary insufficiency. Both of these variables were found to be distributed significantly differently in patients without complications and those with complications, even using the univariate technique ($P<0.01$ and $P<0.02$ respectively) (Henriksson and Johansson, 1987).

ST-segment depression during exercise has been widely used as a marker of myocardial ischaemia, and hence coronary atherosclerosis. The sensitivity of a near-maximal exercise test for coronary artery disease is known to range between 60 and 70% when only ST-segment depression is considered. The specificity of ST-segment depression as an expression of coronary insufficiency is about 90%. It seems highly plausible that an indication of coronary atherosclerosis—in patients without overt clinical cardiovascular disease—before the institution of therapy might be a predictor of such cardiovascular complications as acute myocardial infarction, unstable angina pectoris and other arterial ischaemic events during oestrogen therapy.

Luteinising hormone has not been known to be associated with cardiovascular events but this hormone seems to be a very effective predictor of cardiovascular side effects during oestrogen therapy. A known function of LH in males is stimulation of the interstitial cells of the testis to produce testosterone. In this context it is interesting to recall that testosterone showed a tendency toward higher values in the group with complications (Henriksson and Johansson, 1987). LH is severely depressed during oestrogen therapy and this might have some bearing on the higher incidence of cardiovascular complications in patients with a high pre-treatment level of LH.

Follicle stimulating hormone and cholesterol were included only in the logistic and linear discriminant analyses. These variables therefore do seem to be weaker predictors of cardiovascular events than LH and ST-segment depression. Further evidence of this is that univariate analyses of the variables showed no significant differences between patients with complications and those without complications. FSH and cholesterol could only be used as predictors in logistic and linear discriminant analyses.

Diastolic blood pressure—in combination with ST-segment depression during exercise and LH—was a discriminating variable in the tree regression. Diastolic blood pressure is a well-known risk factor for cardiovascular disease and thus it is conceivable that diastolic blood pressure is included. Diastolic blood pressure is included as the third discriminating variable in the tree regression and this, along with the absence of diastolic blood pressure in the linear discriminant function and the logistic regression, indicates that diastolic blood pressure might be a weaker discriminator than LH and ST-segment depression during exercise.

A further variable, triglycerides, was included in the tree classification. The statistical implication of this variable is that a patient with a high concentration of triglycerides should not be at risk of cardiovascular complications. However, the medical implication that a high triglyceride value should be a non-risk indicator does not make sense. We therefore recommend that triglycerides should be deleted from the tree classification. This results in reduced specificity of the tree classification, but the sensitivity is maintained. We feel that this conservative approach is probably a wise one in this situation.

The result of the tree classification technique is a practical discriminating flow chart (Fig.) that enables rapid and efficient identification of patients at high risk of cardiovascular complications if oestrogen therapy is administered. Those patients predicted to be at risk should be recommended an alternative form of treatment, such as orchiectomy or perhaps luteinising hormone releasing analogues. All that is required of the patient prior to the use of the flow chart is an exercise stress test, a blood test for LH and a measurement of the diastolic blood pressure.

In summary, the discriminating techniques, linear discriminant analysis, logistic regression and tree classification, allowed us to identify 2 strong discriminating variables for cardiovascular complications if oestrogen therapy is instituted in patients with prostatic cancer without overt clinical cardio-

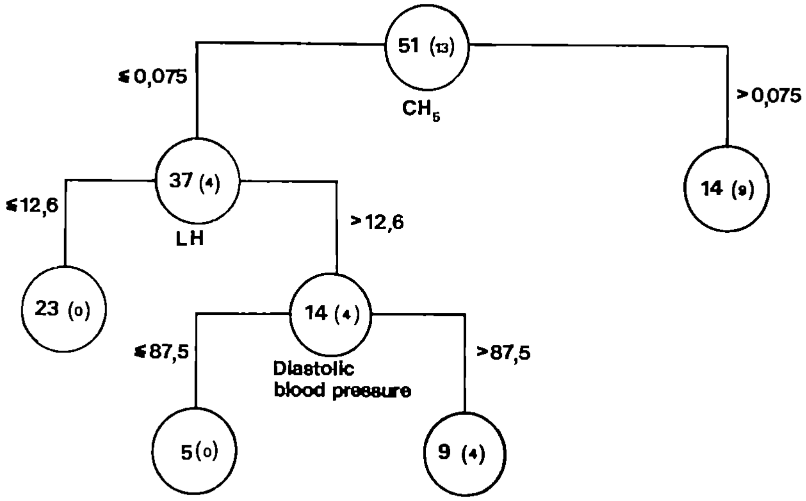

Fig. Classification tree based on 51 oestrogen-treated patients with prostatic cancer. Figures in parentheses indicate the number of patients with complications. CH$_5$ denotes ST-depression in lead CH$_5$ during the exercise stress test (≤ 0.075 mV or > 0.075 mV)

vascular disease. Those discriminators are LH and ST-segment depression during exercise testing. This means that a patient with ST-segment depression during an exercise test and/or a high LH concentration should not be treated with oestrogen. We have presented a practical flow chart for the evaluation of risk of cardiovascular disease when hormonal treatment is indicated.

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Retrospective Study of Radiotherapy in Early Carcinoma of the Prostate

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Summary—During the years 1978 to 1983 there was a 10-fold increase in the number of patients with T1–T4 NX M0 carcinoma of the prostate referred to the Christie Hospital for radical radiotherapy. A retrospective survey of 170 patients treated during this period showed an overall age-corrected 5-year survival rate of 49%. The survival of patients in whom referral for radiotherapy had been delayed was 37% compared with 56% for those given immediate treatment. Patients with poorly differentiated tumours had a significantly reduced survival compared with those with well differentiated tumours. The overall complication rate from radiotherapy was 4% and this low rate is attributed to the small volume used uniformly for treatment.

Carcinoma of the prostate is common, with an incidence in the North West Region of England of 38.6/100,000. Although many patients have disease which progresses slowly, if at all, the mortality rate remains high—23.6/100,000. Until recently the management of early prostatic carcinoma in the N.W. Region (following surgery for obstructive symptoms) usually consisted of hormonal therapy using either stilboestrol or Honvan. However, oestrogens have been shown to increase the morbidity and mortality from cardiovascular disease (VACURG, 1967; Henriksson and Edhag, 1986). Newer hormonal treatments have fewer complications but have not been shown to be more effective and bilateral orchiectomy may be unacceptable to some patients. Although carcinoma of the prostate has previously been regarded as radio-resistant (Patterson, 1942), it has also been known that radiation readily relieves the pain of metastatic bone disease. During the period 1978 to 1983 there was a change in the referral pattern in the North West Region, with increasing numbers of patients being referred to the Christie Hospital for radical radiotherapy to the primary tumour. A retrospective survey of these patients was therefore undertaken to assess the value of radiotherapy and to help in planning future studies.

Patients and Methods

During the period 1978 to 1983, 170 patients with T1–T4 N0 M0 carcinoma of the prostate were referred for radical radiotherapy to the primary tumour. The number referred annually rose from 5 in 1978 to 56 in 1983 (Fig. 1). Numbers have continued to rise—113 in 1984 and 151 in 1985—and now constitute approximately one-fifth of all newly diagnosed cases within the Region. Recent patients have not been analysed in this study because of the short follow-up time. In the first part of the period, referral for radiotherapy was delayed in many patients. Thirty-six received hormonal

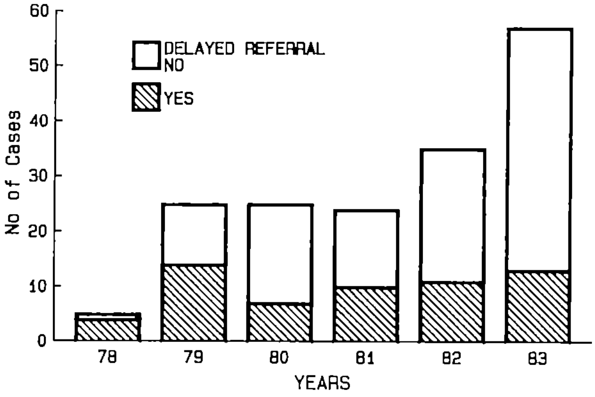

Fig. 1 Numbers of patients referred annually.

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treatment (oestrogen therapy (33), orchiectomy (7), both (6)) and 13 patients underwent a period of observation. Referral for radiotherapy in these patients followed evidence of progression of disease. Latterly, the majority of patients were referred immediately after diagnosis (Fig. 1). Three patients were aged less than 50 years, 23 aged 51 to 60, 84 aged 61 to 70, 57 aged 71 to 80 and 3 more than 80. All patients had chest radiology, isotope bone scan or skeletal survey before referral and the results of acid phosphatase examination were available in 95 patients, 14 of whom had values above the normal range. Assessment of the primary tumour was based on clinical examination at examination under anaesthesia (EUA): 8 patients had T1 tumours at the time of referral, 93 T2, 37 T3 and 32 T4. Histological verification was available in all patients, material generally being obtained by transurethral resection at EUA. The tumour was classified as poorly differentiated in 45 patients, of which 26 were T2, 11 T3 and 8 T4.

Follow-up was undertaken either at peripheral radiotherapy clinics or by the referring surgeon. Patients were seen 6 weeks after completion of radiotherapy and then 3-monthly. Assessment was by clinical examination, isotope bone scan and acid phosphatase examination. Some degree of proctitis, frequency and dysuria was regarded as a normal radiation reaction but this was classified as a minor complication if it persisted beyond 4 weeks of completing radiotherapy or necessitated readmission for nursing care. Complications were regarded as major if the patient required definitive surgery for bowel or bladder complications. Evidence of progression of the primary tumour was obtained by digital examination. It was not possible to assess response in terms of reduction in T staging and repeat biopsies were rarely carried out. Owing to variations in the frequency of the follow-up investigations between different clinics, time to relapse could not be used as a method of assessment. The cause of death was established from hospital records. When this was not possible, death was assumed to be due to prostatic cancer. Survival curves were calculated using the life table method and the log rank test was used to compare survival in different groups (Peto *et al.*, 1977).

Radiotherapy

Localisation for treatment planning was carried out using a marker cystogram, except in 14 patients treated in the latter part of the period in whom computed tomography was used. Radiotherapy was directed to the prostate gland only and no attempt was made to treat the pelvic lymph nodes. A wedged rotation in two arcs of 140° from a 4 or 8 MV linear accelerator was used. The volume irradiated was in the range 7 × 7 × 7 cm to 9 × 9 × 9 cm. In the majority of patients a tumour dose of 5000 cGy was delivered in 16 fractions over 21 days but a few elderly patients received radiotherapy in 8 fractions over 10 days.

Results

All patients completed the prescribed radiotherapy except for 1 who died suddenly of a myocardial infarction shortly after commencing treatment. The doses received are shown in Table 1; 16 patients are currently alive with no clinical evidence of recurrence, 11 have active disease, 18 have died of unrelated causes and 67 from carcinoma of the prostate. In 8 patients the cause of death could not be reliably determined and these patients were assumed to have died from tumour. The life table survival at 5 years for the 169 patients who completed radiotherapy was 49%, but there is no evidence of a plateau in the curve (Fig. 2). The survival of 59 patients in whom referral for radiotherapy was delayed was 37% compared with 56% for 110 patients given immediate radiotherapy ($P = 0.001$) (Fig. 3). The survival by T stage for patients given immediate radiotherapy is shown in Figure 4. The survival of 6 T1 patients was 100% but there was no detectable difference in survival for patients in stages T2, T3 and T4 ($P > 0.15$). In patients in whom referral was delayed, however, survival in T4 patients was significantly worse ($P < 0.001$) (Fig. 5). The survival of patients whose tumours were poorly differentiated was significantly worse—23% at 5 years—compared with 60% for well differentiated tumours ($P < 0.0001$). In the delayed referral group the survival of patients with poorly differentiated tumours was 13% compared with 45% ($P < 0.0002$) (Fig. 6) and in the immediate treatment group 27% compared with 68% ($P < 0.0001$) (Fig. 7). Survival was not affected either by age ($P < 0.3$) or by the serum acid phosphatase level at presentation.

Table 1 Radiation Doses Received

Dose (cGy)	*No.*	*Fractions*
<3000	1	1*
3000–3750	13	8
4750	2	16
5000	152	16
>5000	2	16

* Patient died after 1 fraction.

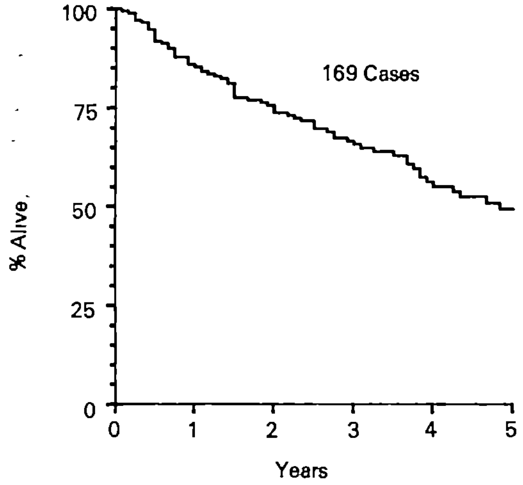

Fig. 2 Survival curve—all patients

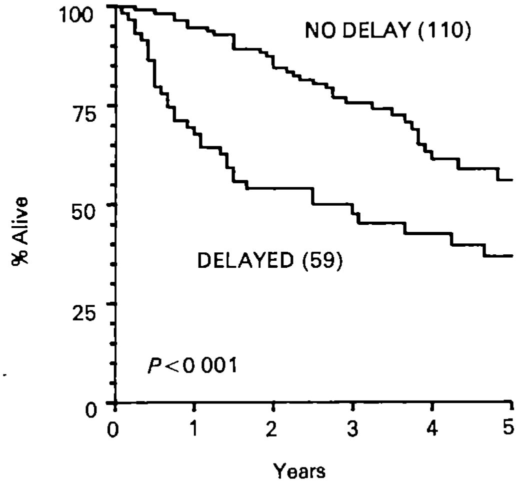

Fig. 3 Survival curve—delayed versus immediate radiotherapy.

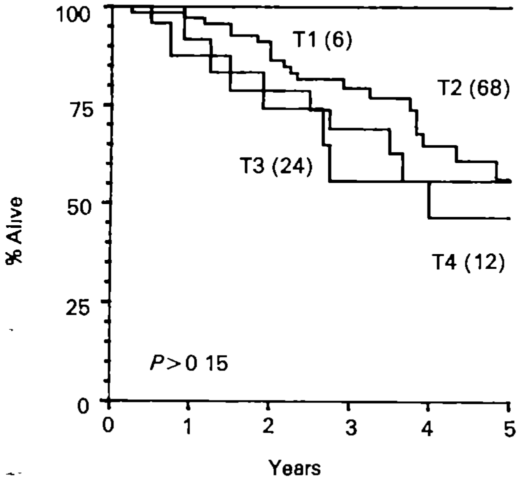

Fig. 4 Survival curve by T stage—immediate referral

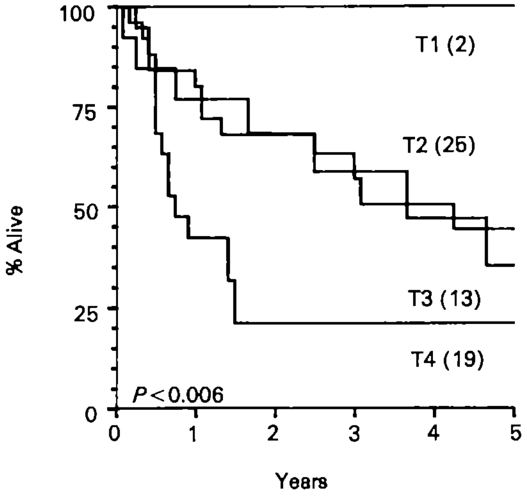

Fig. 5 Survival curve by T stage—delayed referral.

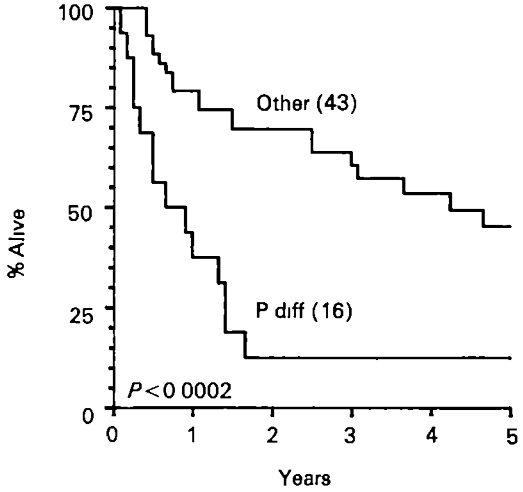

Fig. 6 Survival curve by tumour differentiation—delayed referral

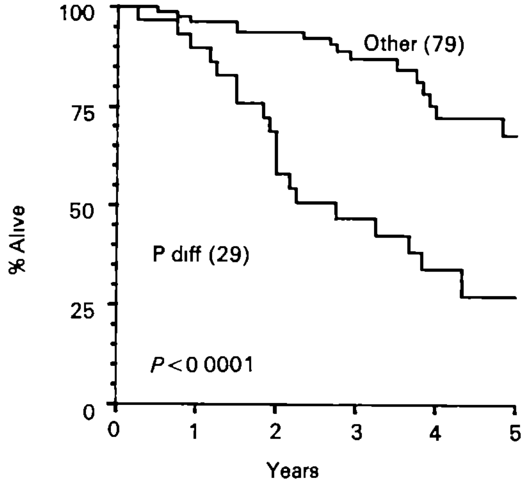

Fig. 7 Survival curve by tumour differentiation—immediate referral

Six patients experienced minor rectal complications and 1 developed renal failure due to bilateral ureteric obstruction within the pelvis. At laparotomy there was extensive pelvic fibrosis. A ureteric reimplantation was performed and the patient subsequently died with widespread bony metastatic disease.

The sites of metastatic disease were lung (3), bone (46) and liver (8). In 23 patients there was evidence of progression of tumour within the pelvis on digital examination. Local progression was associated with the T stage at the time of radiotherapy (Table 2) but was low in T1 and T2 tumours; 12/123 patients (10%) with well differentiated tumours showed progression of pelvic disease compared with 11/45 (24%) with poorly differentiated tumours; 5/16 patients (31%) receiving less than 5000 cGy had local progression compared with 18/154 (11%) receiving 5000 cGy or more. In the absence of lymphography or CT scanning it was impossible to identify nodal relapse as distinct from progression of the primary tumour, but only 2 patients had clinical symptoms suggestive of nodal disease. Local progression was associated with distant metastasis in 75% of cases.

Table 2 Local Tumour Progression versus T Stage at Treatment

T stage	*No*	*%*
T1	0/8	0
T2	6/93	6
T3	8/37	22
T4	9/32	28
Total	23/170	13

Discussion

This study confirms the effectiveness of radiotherapy as a means of local control for prostatic carcinoma. In a recent study of 120 patients managed conservatively, George (1988) found evidence of an increase in local tumour size in 84%. In this study, local tumour progression occurred in only 6% of patients with T2 tumours and although higher in T3 and T4 tumours, 87% of all patients remained free of clinical disease in the pelvis. Comparison with other reported series is, however, difficult. Staging systems differ, depending upon whether or not lymphography was undertaken. Many American series included surgical staging in some of the patients or radiotherapy was given only where radical surgery was incomplete (Jacobson *et al.*, 1987). Local relapse rates are not always reported because of the difficulty in assessing the prostatic bed after a radical course of radiotherapy.

This study differs from previously reported series in the dose and field size used. Most series have used longer fractionation and times in the range 6000 to 7000 cGy in 5 to 6 weeks (Bagshaw, 1979), although 4-week treatment times have been reported by Hope-Stone (1987) and Preston *et al.* (1986). Although the doses are radiobiologically not dissimilar, the shorter time employed in this series has major advantages in centres where machine time is limited.

In many series, fields large enough to include the whole pelvis, and occasionally the para-aortic nodes, have been used in all or selected patients (Table 3). In this series a uniformly small field size has been used in all stages. Although McGowan (1981) reported a survival advantage for extended field irradiation in patients with locally advanced primary tumours, this has not been found by other workers (Harisadis *et al.*, 1978). This is surprising, since pelvic nodal involvement is well recognised as a prognostic factor (Bagshaw, 1985). Symptomatic relapse in the pelvis is unusual and when relapse occurs the clinical picture is generally dominated by bone and other distant metastases. In the study by Rounsaville *et al.* (1987) only 4% of patients had symptomatic nodal failure.

The major determinant of survival in this study was the histological differentiation of the tumour and this has been recognised in earlier studies (Gleason and Mellinger, 1974). Well differentiated tumours had a life table 5-year survival rate of 60% compared with 23% for poorly differentiated tumours. Survival was particularly poor in patients with poorly differentiated tumours in whom referral was delayed, with 65% dead at the end of the first year. In all groups delayed referral was an adverse factor and this accords with the retrospective study of Preston *et al.* (1986) and in the reports cited by Hafermann (1988). Patients with T1 tumours had a 100% relapse-free survival. Some authors have advocated conservative management only in this group of patients (Heaney *et al.*, 1977) but the number of patients referred in this subgroup was too small for comment. There was little difference in survival between patients staged T2, T3 and T4, except for patients with T4 tumours in whom referral was delayed. This may imply that clinical staging is inaccurate and improved staging methods are required.

Since it is impossible to irradiate the prostate without including part of the rectum, virtually all patients receiving radiotherapy experience some

Table 3 Radiotherapy for Carcinoma of the Prostate: Review of the Literature

Authors	*No. of patients*	*Treatment*	*Severe complications*	*Pelvic relapse*	*5-year survival*			*10-year survival*		
					*T2**	*T3†*	*All*	*T2**	*T3†*	*All*
Preston *et al.* (1986)	116	Various techniques	6		80	45	60			32
Bagshaw (1985)	879	Pelvic irradiation Surgical staging			81	62		59	36	
Rounsaville *et al.* (1987)	251	Limited field radiotherapy	0	15	84	63	71	53	42	50
Rosen *et al.* (1984)	229	Limited field radiotherapy	1.6	16	75	60				
		Pelvic irradiation	8.7	12	78	52				

* or stage B equivalent † or stage C equivalent.

proctitis and it is difficult to define what constitutes a "normal" or acceptable reaction. However, with the technique employed in this series the complication rate was low and this may be attributed to the small volume irradiated. Several authors (Rosen *et al.*, 1984; Preston *et al.*, 1986; Rounsaville *et al.*, 1987) have reported increased complications in patients in whom the whole pelvis has been irradiated.

Even at 5 years, however, patients continue to die from prostatic cancer and radiotherapy may only provide a means of local control. Radiotherapy, however, has a low complication rate (4% in this study) compared with oestrogen therapy and is more effective than other hormonal manipulations. It provides a satisfactory means of controlling disease within the prostate, especially in T2 (6% relapse) and well differentiated tumours (10% relapse). Further studies are required to determine whether or not the addition of hormonal procedures would improve the survival of patients with poorly differentiated tumours.

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Balanitis

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Summary—The clinical features of 100 cases of balanitis are described. The condition affects no more than 4% of boys, is commonest during pre-school years (but rare prior to toilet training) and is usually associated with a prepuce which is partly or completely non-retractable. It does not cause phimosis and no single pathogen is involved. Most boys suffer a single episode and circumcision is indicated only for those with recurrent, troublesome attacks.

Acute balanoposthitis or, more popularly, balanitis, is a common complaint of boys yet one which receives no more than cursory attention in textbooks and none in the literature otherwise. We make a modest attempt to remedy this deficiency.

Patients and Methods

We report 100 consecutive boys seen in our clinic over a 3½-year period with a diagnosis of balanitis; 32 had presented acutely to the Accident and Emergency Department, when a swab of purulent discharge from the preputial orifice had been obtained for bacteriological examination. In order to assess the incidence of the condition, we questioned 200 consecutive boys aged 7 to 14 years passing through the out-patient clinic for a history of balanitis; excluded were those previously circumcised for other reasons.

Results

Incidence

Of the 200 boys questioned, 3 had definitely had balanitis and 5 gave a history suggestive of the disease.

Age distribution

Most were aged 2 to 5 years; only 5 boys were not toilet trained. Three were under 2, 15 were either 6 or 7 and 6 were either 8 or 9.

Symptomatology (Table 1)

A history of purulent discharge from the preputial orifice was regarded as pathognomonic of balanitis; in the absence of this feature, a combination of redness and swelling of the prepuce was considered compatible with the diagnosis provided there was no evidence of ammonia dermatitis, allergy or mechanical irritation of the foreskin ("foreskin fiddling"). Among the few complaining of dysuria, other symptoms of urinary tract infection were lacking.

Physical signs

One patient had true phimosis. The only other finding of note was the state of retractability of the prepuce, which was non-retractable in 30 cases, partially retractable in 57 and fully retractable in 13.

Recurrence

A single attack of balanitis was recorded in 64 boys. At the time of writing, which extends from 0.6 to 4.1 years (mean 2.3) after they had been seen, only 2 have returned with a second episode despite a general invitation to reattend if there were further

Table 1 Symptomatology

Redness	100
Swelling	91
Discharge	73
Dysuria	13
Bleeding	2
Glans ulceration	1

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Table 2 Management

No of episodes	*No of patients*	*Circumcision*
1	64	7
2	20	13
3 or more	16	15

problems. Only a small minority (Table 2) had suffered 3 or more episodes.

Bacteriology

Among the 32 patients presenting acutely, culture of discharge from the preputial orifice showed no growth in 15 cases, a mixed growth in 7 and a pure growth of a single organism in 10 (5 *Staph. aureus*, 4 *Proteus vulgaris*, 1 *Morganella morgagni*).

Management (Table 2)

The usual policy was to recommend circumcision in the event of 2 or more episodes; 6 of the 7 boys circumcised for a single attack had this performed at the parents' request.

Discussion

Although balanitis is a common complaint, the risk in any individual, uncircumcised boy appears to be no greater than 4% and even this is appreciably more than the 1% who develop true phimosis (Oster, 1968; Rickwood *et al.*, 1980) or the very few with paraphimosis (Gairdner, 1949). A policy of routine neonatal circumcision to avoid these preputial complaints of childhood would be difficult to justify. We found no evidence that balanitis causes phimosis.

Diagnosis outside the acute stage cannot always be certain and some patients in this series may not have had true balanitis. Ammonia dermatitis is usually easy to exclude, but "foreskin fiddling", a habit indulged in by not a few young boys, may be mistaken for balanitis.

The aetiology remains unresolved. There is no single causative pathogen, nor is it proven that the suppurative process is necessarily of bacterial origin. Its rarity amongst boys in napkins suggests that some component of urine, or of its breakdown products (possibly ammonia), affords protection. Beyond infancy, the age distribution corresponds with that period when the foreskin is partially or completely non-retractable due to persistence of preputial adhesions and there is logic in the proposition that this predisposes to lodgement of pathogens beneath the foreskin. That said, the incidence of incomplete retractability of the foreskin in patients in this series was no greater than is normally found in young boys (Gairdner, 1949; Oster, 1968), nor is a fully retractable foreskin proof against balanitis. Poor personal hygiene would seem an obvious factor, although we are not impressed that this is the case.

As for management, once the acute episode has been treated, active measures seem unnecessary for boys with a single attack since most will suffer no more. For those with multiple episodes, we take the idiosyncratic view that "preputial stretching" and "freeing of adhesions", with or without general anaesthesia, are wholly useless procedures. Other surgeons are of the opposite persuasion and until the improbable event of a clinical trial, this issue, like so many in surgery, must remain more a matter of faith than fact. The age distribution of our patients indicates that balanitis is ultimately a self-limiting condition and most patients could probably be managed expectantly. Nonetheless, we consider that circumcision is justified for boys with recurrent attacks of balanitis causing appreciable discomfort.

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Retrograde Ejaculation: Successful Treatment with Artificial Insemination

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Summary—Between 1977 and 1987, 14 couples in whom the male partner had retrograde ejaculation were treated with artificial insemination using the husband's sperm (AIH). There were 6 pregnancies in 4 couples, giving a cumulative probability of pregnancy at 12 months of 72%. The success rate depended on a number of factors, including semen quality, methods of sperm extraction from the urine, timing of ovulation and other complicating fertility factors.

Retrograde ejaculation may be defined as the escape of seminal fluid from the posterior urethra into the bladder with retention of sensation of orgasm. The seminal fluid reaches the posterior urethra but patency of the bladder neck results in retrograde flow.

The aetiology of this condition may be congenital or acquired. Surgical procedures which distort the anatomy or physiology of the junction between the posterior urethra and bladder can lead to retrograde ejaculation. Transurethral resection of the prostate (TUR) is a common cause of retrograde ejaculation, which was reported in 42% of sexually active men following this procedure (Rieser, 1961). There is also an association between diabetes mellitus and retrograde ejaculation mediated via a peripheral neuropathy (Greene and Kelalis, 1968). It can occur following trauma, thoracolumbar sympathectomy, abdominal-perineal resection, retroperitoneal lymphadenectomy, certain lesions of the spinal cord and the administration of certain drugs, *e.g.* guanethidine. Idiopathic cases have also been described (Sandler, 1979). The diagnosis is made from the history (absent or intermittent emission of semen, orgasm without visible ejaculate, the ability to void urine during erection) and may be confirmed by finding sperm in post-coital specimens of urine.

Treatment for the associated infertility is warranted. Sympathomimetic drugs may achieve antegrade ejaculation (Stockamp *et al.*, 1974; Sandler, 1979; Virupannavar and Tomera, 1982) and successful pregnancy has been reported. Ejaculation with a full bladder may in some cases result in antegrade ejaculation (Crich and Jequier, 1978). Artificial insemination of sperm from post-orgasmic urine was initially described over 30 years ago (Fischer and Coates, 1955) and since that time further cases have been reported. More recently, the insertion of sperm reservoirs followed by removal of sperm from the reservoir combined with AIH has resulted in pregnancy (Brindley *et al.*, 1986).

Patients and Methods

At Chelsea Hospital for Women from 1977 to 1987, 20 couples with a primary diagnosis of complete retrograde ejaculation presented to the infertility clinic. In all cases the diagnosis was confirmed by finding sperm in post-coital samples of urine. In 3 couples the sperm quality was extremely poor and they were advised to consider other methods of treatment. A further 3 couples are waiting for treatment. The remaining 14 couples have been treated by artificial insemination with husband's sperm (AIH).

The aetiology of the retrograde ejaculation is shown in Table 1. The mean age of the male partner was 34 years and that of the female 28 years. The female partner was investigated to exclude other major causes of infertility. This included confirma-

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

Table 1 Causes of Retrograde Ejaculation, Age and Other Fertility Factors in 14 Couples

Patient no.	*Diagnosis*	*Age of male partner*	*Age of female partner*	*Other factors*
1	Congenital	34	27	Nil
2	Congenital	27	26	Nil
3	Congenital	29	28	Nil
4	Diabetes	31	22	Nil
5	Diabetes	28	27	Nil
6	Diabetes	28	28	Nil
7	Diabetes	28	25	Nil
8	Diabetes	36	29	Nil
9	Bladder papilloma	30	27	Nil
10	Panproctocolectomy	33	30	Nil
11	Hypertrophy of bladder sphincter	35	30	Anovulation
12	Seminal vesical cyst	33	26	Nil
13	Post-TUR	69	39	Poor luteal phase
14	Post-TUR	39	26	Anovulation

tion of ovulation and assessment of tubal patency by either hysterosalpingography or laparoscopy with hydrotubation. An ovulation disorder was established in 3 couples and they were treated with clomiphene citrate (Clomid, Merrell Dow).

The expected time of ovulation was estimated in most cases by previous cycle length and basal temperature charts. In 10 cycles, ovulation was predicted either by ultrasonography, looking at follicular diameters, or by detection of the rise in luteinising hormone (LH) measured in urine. Two to 3 days before planned insemination, the male partner was instructed to take sodium bicarbonate tablets 1.2 g *bd* in an attempt to raise the normal acid pH of the urine.

Instructions concerning the sample production on the day of insemination were as follows. The patient was asked to empty the bladder completely and then to masturbate. After a period of 15 min he was asked to urinate into a sterile container for immediate transfer to the seminology laboratory. The sample was immediately checked for the presence of sperm. The pH of the urine was ascertained and adjusted if necessary to pH 7.2 by the addition of 5% sodium bicarbonate.

In some cases the urine itself was used for insemination. In others the sperm was extracted from the urine and resuspended in a variety of different culture media, *e.g.* Hanks solution, Hams F10, Earles solution or 4% human serum albumin (HSA). Following centrifugation at 2000 rpm for 5 min, the sediment was resuspended in medium and centrifuged again. The sediment was then finally suspended in 2 to 3 ml of medium ready for insemination.

Insemination was performed once or twice per cycle. In all cases where urine was used, intracervical insemination was performed using a syringe and Kwill. In a few cases intrauterine insemination was performed.

Results

The results of treatment are summarised in Table 2. A total of 86 cycles were initiated and couples received between 1 and 11 cycles of treatment. There have been 6 pregnancies in 4 couples, all of which resulted in the full-term delivery of a normal child. Of the 6 pregnancies, 4 followed insemination of sperm suspended in 4% HSA and 2 followed insemination of urine. The pregnancy rate per cycle was 7% and the pregnancy rate per patient was

Table 2 Sperm Quality, Methods of Sperm Preparation, Number of Treatment Cycles and Outcome in 14 Couples

Patient no.	*Sperm quality*	*No of cycles*	*Medium/urine*	*Pregnancy*
1	Good	9	Hanks-6,4%HSA-3	Yes
		1	4%HSA-1	Yes
2	Good	5	4%HSA-5	Yes
		7	Urine-2,4%HSA-5	Yes
3	Poor	8	Urine-3,Earles-5	No
4	Good	1	4%HSA-1	No
5	Poor	10	Urine-4,4%HSA-6	No
6	Variable	11	4%HSA-6,Urine-5	Yes
7	Poor	1	Earles-1	No
8	Poor	2	Earles-2	No
9	Good	2	4%HSA-2	No
10	Poor	5	HAMSF10-5	No
11	Good	11	4%HSA-3,Urine-8	No
12	Good	2	4%HSA-1,Urine-1	Yes
13	Poor	5	4%HSA-2,Urine-3	No
14	Poor	6	4%HSA-6	No

28%. As some patients received only very few cycles the results were analysed to give a cumulative probability of pregnancy: this was 72% at 12 months. Of the 3 patients whose aetiology was congenital, 2 conceived on 2 occasions; 1 of the 5 diabetic couples achieved a pregnancy on the eleventh cycle of insemination. The couple with a seminal vesical cyst conceived on the second cycle of treatment and conceived again subsequently following the insertion of sperm reservoirs combined with AIH.

Discussion

Retrograde ejaculation is a rare cause of infertility and it can be successfully treated by AIH. Several factors appear to influence the likelihood of success, the most significant being sperm quality and quantity. In 6 of our 14 couples the semen parameters were good. Pregnancy occurred in 3 of these 6 patients. Of the 3 who failed to conceive, 2 received only 1 or 2 cycles of treatment and the other had an ovulation disorder.

The sperm parameters are often related to the aetiology of the condition. Diabetic patients often have poor quality sperm (Bourne *et al.*, 1971). We achieved only 1 pregnancy amongst 5 couples with diabetes. This particular patient had very variable semen quality and conceived on the eleventh cycle of treatment, when urine was used for insemination. When the semen quality is consistently poor the couple should be advised about alternative methods of treatment, *e.g.* artificial insemination using donor sperm (AID).

There is little one can do to improve sperm quantity but attention to detail may help to maintain or enhance sperm motility. Firstly, it has been observed that a low pH is detrimental to sperm survival (Crich and Jequier, 1978). We therefore advocate the use of pre-treatment with sodium bicarbonate and prompt adjustment of the pH of the urine to 7.2. Secondly, it may be advantageous to resuspend the sperm in an environment which maintains or enhances sperm motility: 4 of the 6 pregnancies occurred using 4% HSA culture medium (Scammell *et al.*, 1982). HSA has been shown to enhance human sperm motility (Suter *et al.*, 1979). Adenosine triphosphate (ATP) is of considerable importance in maintaining sperm motility. HSA appears to have its effect by increasing the efficiency of ATP coupling. Unfortunately, there is now concern about the use of pooled serum in view of the theoretical risk of transfer of the AIDS virus and a reasonable alternative would be to use serum from the female partner (Ingerslev, 1985). One factor which can be influenced is accurate prediction of the timing of ovulation. It was interesting to note that of the 86 cycles described only 7 were timed with urinary LH. One of the 6 pregnancies occurred in the seventh cycle of treatment, which was associated with a change of timing method from basal temperature charts to urinary LH. Several ovulation predictors are now commercially available, based on radioimmunoassays of LH in the urine, and these kits seem to be of benefit in improving the success rates of AIH. Urry *et al.* (1986) showed a 16% pregnancy rate per cycle with LH-timed intrauterine insemination using washed sperm. We did not analyse the differences between intracervical and intrauterine AIH. Clearly there are potential problems related to intrauterine insemination, such as uterine spasm and infection.

Other factors which may influence the outcome of treatment are related to the female partner and the presence of other fertility factors will lead to lower rates of success: no pregnancy occurred in the 3 couples in whom an ovulation disorder was diagnosed.

In conclusion, retrograde ejaculation leading to failure to conceive can be successfully treated with AIH. It is most likely to succeed when the semen quality is favourable, when there are no other complicating fertility factors and accurate methods of timing ovulation are used.

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Proteinuria—What Value is the Dipstick?

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Summary—The value of the urinary dipstick in the assessment of proteinuria was investigated in a study correlating laboratory measurements of protein and albumin against the dipstick protein in the same samples of urine; 94 patients (100 admissions) were studied at the Royal Air Force Renal Unit, each patient collecting two 24-h urine samples. Along with each 24-h sample, 10-ml aliquots of urine were obtained at 3 designated times during the day for both ward dipstick testing and laboratory assay; + or more on the dipstick correlated with abnormal proteinuria ($\geqslant$ 150 mg/24 h) in 88% of cases, whilst trace values straddled the level of significant proteinuria. Further differentiation of trace was possible by repeat testing during the day. The subsequent presence of a dipstick negative during that day correlated with normality in all but 5% of cases.

In order to ensure detection of renal disease presenting as isolated orthostatic proteinuria, assay of the mid-morning sample is recommended.

Urine dipsticks have been widely advocated as an adjunct to diagnosis in the consulting room. The detection of asymptomatic proteinuria at screening or insurance medicals is common and merits investigation if present in significant quantities. The early detection of proteinuria at low levels is important in conditions such as systemic lupus erythematosus, diabetes mellitus and pregnancy. Dipsticks are regarded by some authors as unreliable for distinguishing abnormality at low levels of proteinuria. This study therefore set out to discover whether the dipstick could discriminate normal from abnormal levels of proteinuria.

The study compared the urinary protein levels recorded, using the N-Multistix SG (Ames Co.) dipstick, with laboratory measurements of urinary albumin and total protein and aimed to determine whether the time of day was important in detecting abnormal amounts of proteinuria. We tested the commonly held belief that small amounts of proteinuria varying with posture can be regarded as benign and due to orthostasis.

Patients and Methods

The study group comprised subjects admitted for routine investigation to the Renal Unit between December 1986 and July 1987. The 94 patients studied (20 female, 74 male, ages 12–69 years) during 100 admissions included both service personnel and civilians suffering from a wide variety of renal conditions, including some patients with no demonstrable renal abnormality.

Each patient collected two 24-h urine specimens and was ambulant during the day. At 3 specified times on each of the 2 days (mid-morning, mid-afternoon and early-morning), separate 10-ml aliquots of urine were collected. These were tested by the ward staff using N-Multistix SG according to the manufacturer's instructions. The N-Multistix SG was chosen because this is the standard dipstick in use throughout the Royal Air Force. The protein results were scored as negative, trace, +, ++, +++ and ++++. If the reading of the stick appeared to fall between two scores, the higher value was recorded. If the urine pH was greater than 7.0, the urine was retested by a doctor after acidification with acetic acid and this result recorded. The 3 aliquots of urine and the 24-h collection were each assayed for albumin, total protein and creatinine by the Clinical Chemistry department.

Laboratory methods

Urine creatinine was measured on a Hitachi 705 analyser using a Jaffe kinetic method without

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deproteinisation, modified from the method of Bartels *et al.* (1972).

Urine total protein was measured on an Ames Optimate analyser using a modification of the automated method of Heick *et al.* (1980), using Coomassie Brilliant Blue.

Urine albumin was measured using an "in-house" immuno-turbidometric method. Freshly constituted goat anti-human albumin (Sigma A1151) was diluted 1 in 50 in phosphate buffered saline (pH 7.4) containing polyethylene glycol 4% (w/v): 50 µl of sample, diluted to give a total protein concentration less than 100 mg/l, were incubated with 500 µl of the antibody solution at 37° C for 15 min. The absorbance was measured at 340 nm. A blank reading was taken by adding the sample to a solution containing 4% polyethylene glycol without antibody.

The albumin concentration was determined from a standard curve using standards in the range 12.5 to 100 mg/l prepared from 500 mg/l human albumin (Sigma A9511) diluted in phosphate buffered saline with 1% bovine albumin added to prevent absorption. This was linear to 100 mg/l. The limit of detection was found to be 6 mg/l but for practical purposes this was taken as 12 mg/l.

Quality control was achieved using human urine spiked with human albumin from a separate source to that used for the standards. The assay precision checks demonstrated within-batch standard deviations of 1.3 mg/l (CV 3.4%) at a level of 38 mg/l and 1.1 mg/l (CV 1.7%) at 64 mg/l. Between-batch standard deviations were 0.5 mg/l (CV 1.7%) at 30 mg/l and 2.23 mg/l (CV 5.4%) at 40 mg/l.

Statistics

Graphical comparison of the dipstick albumin and total protein readings with the corresponding laboratory assay values was effected using "Box and Whisker" plots (Hartwig and Dearing, 1979). This standard technique of exploratory data analysis highlights the region in which the central 50% of dipstick values fall—the "Box". The spread of the remaining dipstick values around the "Box" is indicated by the "Whiskers", the construction of which permits an empirical identification of atypical dipstick results at any given test level (neg, trace, +, + +, + + +, + + + +).

The degree of association in the ordered contingency tables (Figs 1 and 2) was assessed using the Goodman and Kruskal gamma-coefficient (Goodman and Kruskal, 1954), a standard measure which can be interpreted approximately as a squared correlation coefficient. It is generally employed as a descriptive measure without regard to questions of statistical significance, being used to compare identically structured tables bearing on a common problem. The coefficient values range from −1 (perfect negative association) through zero (no association) to +1 (perfect positive association).

Results

A total of 94 patients entered the study, with 4 patients entered twice and 1 entered thrice. All completed the protocol.

In those with a urine pH greater than 7, acidification did not alter the final dipstick reading for protein.

The 600 urinary dipstick protein values were plotted graphically, using the "Box and Whisker" method, against both total protein and albumin concentrations from the laboratory (Figs 3 and 4). These graphs reveal the poor discrimination between negative and trace dipstick readings in relation to the corresponding laboratory values and reveal the relatively high discriminatory value around the "trace or less/+ or more" boundary.

Each patient's 6 dipstick protein values were then tabulated against their corresponding 24-h urine protein and albumin values and the Goodman and Kruskal coefficients calculated (Figs 1 and 2). The results revealed a common degree of association across all 6 tables (*i.e.* no statistically significant difference between the 6 sample coefficients). This would suggest that the time of testing for urinary protein is of no practical importance.

This rather surprising finding prompted a search for variation in the degree of proteinuria within individual cases. A "practically significant" variation was present if during the 24-h test period, values of dipstick protein bridged the "trace or less/+ or more" boundary. Using this criterion, significant variation was present in 17 of the 100 cases over the 2 days and in 8 of these cases on both days; 13 of these 17 cases had proteinuria which was trace or less in the early-morning urine and + or more whilst ambulant—an orthostatic picture. Of these 17 patients, however, 10 also had dipstick haematuria and in all 10 this correlated with significant renal lesions. Of the remaining 7 patients, postural proteinuria was an isolated finding and in 5 of the 7 was considered benign (Table 1).

Discussion

Abnormal levels of urinary protein excretion have been variously defined as 25 to 75 mg/24 h by

Dipstick 1

Albumin mg 24 h^{-1}	NEG	Tr	+	++	+++	++++
>7500			1		2	7
−7500			2	3	9	2
−1000	5	5	4	10	2	
− 200	7	4	2			
− 100	5	3	1			
< 50	15	10	1			

$\gamma=0.79$

Dipstick 4

				2	7
		1	6	9	1
3	5	5	5	2	1
3	10	4	1		
3	9		1		
11	10	1			

$\gamma=0.81$

Dipstick 2

				3	7
		2	5	7	2
9	5	8	3	1	
7	6				
5	4				
17	8	1			

$\gamma=0.79$

Dipstick 5

			1	1	7
		1	7	8	1
5	8	4		3	
6	10	3			
7	5		1		
12	10				

$\gamma=0.76$

Dipstick 3

				1	9
		3	4	9	
5	8	11	1	1	
3	7	3			
4	4		1		
12	13	1			

$\gamma=0.80$

Dipstick 6

				4	5
	1	2	5	8	1
5	7	4	1	3	
3	14	1	1		
5	8				
13	8	1			

$\gamma=0.79$

γ = Goodman–Kruskal coefficient of association (−1 to +1)

Fig. 1 Ordered contingency table for laboratory albumin values versus numbers of dipsticks positive at each test level. γ = Goodman–Kruskal coefficient of association (−1 to +1) Dipsticks 1 and 3 are mid-morning, 2 and 4 are mid-afternoon, 3 and 6 are early-morning.

Dipstick 1

Total protein g/24 h	NEG	Tr	+	++	+++	++++
>3.0				1	7	8
−3.0			3	2	5	1
−1.0	1	2	3	8		
−0.5	3	3		1	1	
−0.3	13	5	3	1		
<0.15	15	12	2			

γ=0.77

Dipstick 4

				9	8
		1	6	3	
	2	3	4	1	1
1	2	1	2		
7	13	4	1		
12	17	2			

γ=0.84

Dipstick 2

			1	9	7
		2	5	1	2
2	2	6	2	1	
5	2	2			
16	6				
15	13	1			

γ=0.75

Dipstick 5

			3	6	8
		1	5	4	
	4	5		2	
2	3		1		
14	9	2			
14	17				

γ=0.79

Dipstick 3

			1	7	9
	1	3	3	3	
2	1	8	1	1	
2	4	3			
7	12	3			
13	14	1	1		

γ=0.79

Dipstick 6

			1	10	6
	1	2	4	3	
2	1	4	2	2	
1	5				
12	13	1			
11	18	1			

γ=0.75

γ= Goodman–Kruskal coefficient of association (−1 to +1)

Fig. 2 Ordered contingency table for laboratory total protein values versus numbers of dipsticks positive at each test level.

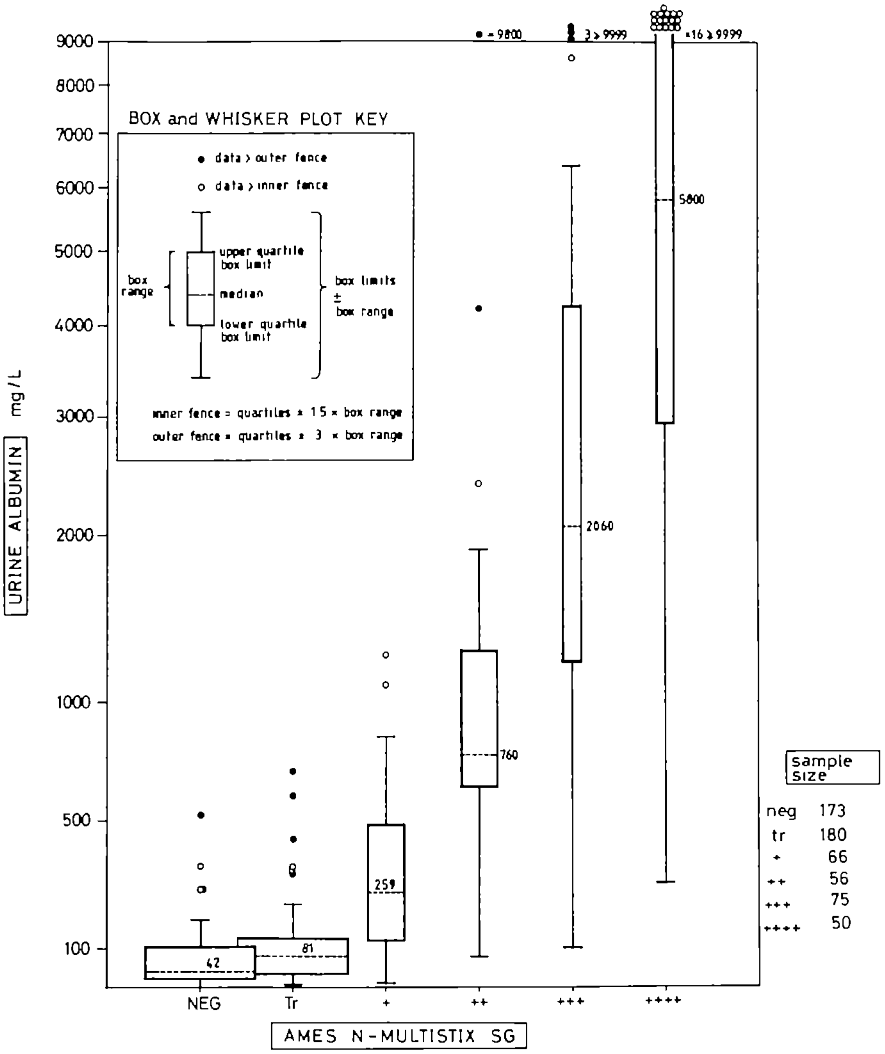

Fig. 3 "Box and Whisker" plot of dipstick protein values (neg, trace, +, ++, +++, ++++) versus the corresponding laboratory values for total protein

Cannon *et al.* (1974), 80±24 mg/24 h by Berggard (1970), 100 mg/24 h by McSwiney *et al.* (1983) and 150 mg/24 h by Borer (1979). Our view is that a level greater than 150 mg/24 h is abnormal.

Shaw *et al.* (1985), using 100 mg/24 h as the cut-off, when comparing Multistix (Ames Co.) with Chemistrip (Biodynamics), concluded that both sticks should be considered positive at the trace level for protein.

Our study shows that for N-Multistix SG there was a considerable overlap of negative and trace values. A dipstick value of + or more was associated with an abnormal 24-h protein excretion of more than 150 mg in 88% of cases (Table 2), but trace cannot be ignored, for 54% of dipsticks at level trace correlated with abnormal proteinuria. However, by the simple expedient of repeat testing throughout that day, the trace positivity was further divisible into abnormal and normal, for if at any time trace became negative, the urine protein was normal in all but 5%. We suggest that a dipstick level of + or more should prompt further investigation. The finding of a trace requires repeat testing to define the abnormal urine.

The problem of identifying the best time of the day to test for a urinary abnormality has recently been examined by Howey *et al.* (1987), using the albumin/creatinine ratio. They concluded that a

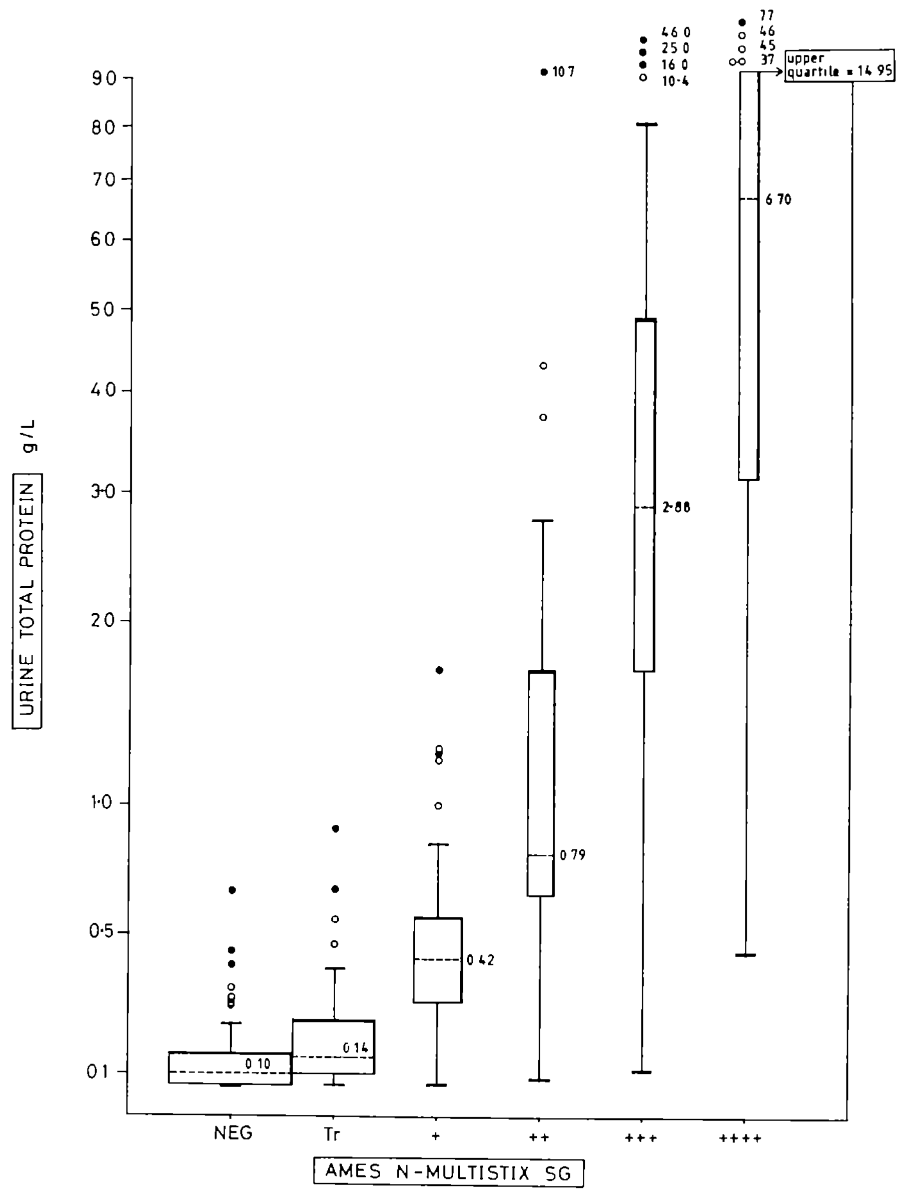

Fig. 4 "Box and Whisker" plot of dipstick protein values (neg, trace, +, ++, +++, ++++) versus the corresponding laboratory values for albumin

"spot" early-morning assay was the most suitable screening test.

Taking the study sample as a whole, and using the dipstick as the sole parameter, our data suggest that the timing of testing is unimportant. On an individual patient basis, however, where in 17 patients dipstick proteinuria crossed the boundary of significance during the day (trace or less/+ or more), it was orthostatic in nature in 14 of the 17, suggesting that by testing only the early-morning urine one would miss some patients with renal disease. This would certainly be the case if one tested the urine for protein alone as with Albustix (Ames Co.).

The danger of screening urine for protein in isolation becomes obvious when one takes into account dipstick haematuria, which was present in 8 of these 14 patients, this being an absolute

Table 1 Variable Proteinuria Suggestive of Orthostasis

Case no.	*Variation (one or both days)*	*Haematuria*	*Diagnosis*
1*	Both	No	Orthostasis
7	Both	Yes	IgA nephropathy
10	One	Yes	Trigonitis
15*	Both	No	IgA nephropathy
16	Both	Yes	IgA nephropathy
19*	Both	No	Orthostasis
20*	One	No	Orthostasis
29*	One	No	IgA nephropathy
34	One	Yes	Nephrolithiasis
35	Both	Yes	Henoch-Schonlein
43	One	Yes	Reflux nephropathy
52	One	Yes	Henoch-Schonlein
83*	Both	No	Post-ARF
93	Both	Yes	Alport's syndrome

*Isolated proteinuria.

Table 2 Dipstick Values

Albumin (mg/24 h)				
Dipstick	%≥50	%≥100	%≥200	
Negative	53.9	38.3	20.4	
Trace	67.9	50.0	21.2	
+	92.3	90.8	72.3	
++	100.0	94.6	87.5	
+++	100.0	100.0	100.0	
++++	100.0	100.0	100.0	
Total protein (g/24 h)				
Dipstick	%≥0.1	%≥0.15	%≥0.2	%≥0.25
Negative	50.9	38.6	16.5	12.3
Trace	67.3	54.1	38.3	29.1
+	93.4	88.5	83.6	83.6
++	98.2	98.2	98.2	96.5
+++	100.0	100.0	100.0	100.0
++++	100.0	100.0	100.0	100.0

indicator of abnormality (Arm *et al.*, 1986). Only 6 actually met the criteria for "benign orthostasis" and 3 of these had renal abnormalities. In order not to miss the small group of patients with a renal abnormality presenting as isolated orthostatic proteinuria, testing should perhaps be performed on mid-morning samples rather than an early-morning urine.

This study has shown the N-Multistix SG dipstick to be a useful semi-quantitative method of assessing the level of proteinuria in both normal patients and those suffering from a wide spectrum of renal disease. The presence of + proteinuria at any time of day requires further investigation. Trace proteinuria should prompt repeat testing during that day, and if persistent or increasing in positivity warrants investigation with a 24-h urine protein estimation.

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Which Urine Sample for Detection of Proteinuria?

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Summary—The standard practice of screening for proteinuria in the concentrated early morning urine was examined. Protein concentration and dipstick readings were determined in early morning and daytime urines of 56 normal subjects and 110 patients with proteinuria attending a renal clinic. In normal subjects the protein concentration was similar in both urine samples and dipsticks gave the same frequency of false positive results, usually only trace positive. The protein concentration was higher in the daytime urine in 76% of patients. Dipstick readings were similar in 64.5% but higher in the daytime urine in 31% and in the early morning urine in only 4.5%. It is recommended that daytime urine should be screened for proteinuria in patients presenting in out-patient clinics.

It is often advised that screening for proteinuria with dipsticks should be performed on early morning urine samples because they are more concentrated (Pryor, 1977; Raman and Lee, 1986), but ambulation can increase protein excretion in normal subjects and in patients with proteinuria (King, 1957). We studied protein concentration and dipstick readings in early morning and in random daytime urine samples.

Patients and Methods

A study was made of 56 normal subjects and 110 patients with proteinuria attending a renal clinic. Young subjects with isolated orthostatic proteinuria were excluded. All patients were attending a morning clinic and the early morning urine was refrigerated until brought to the clinic. The daytime urine was passed at the clinic. Protein excretion was determined by a 24-h collection or by a protein-creatinine index (Shaw *et al.*, 1983). Ames Multistix + SG dipstick readings were performed in the laboratory using the Ames Clin-Tek photometer.

Results

The mean 24-h protein excretion was 79.6 mg in normal subjects. The protein concentration was higher in 32 (57%) daytime samples and 24 (43%) early morning samples ($P > 0.10$); the mean protein concentration was similar in both samples (Table). The dipstick gave 13 (23%) false positive readings in the daytime samples and 16 (29%) in the early morning samples ($P > 0.10$). Of the false positives, 23 were trace and 6 were (+) positive samples; 3 of the latter were in early morning and 3 in daytime urines.

The mean 24-h protein excretion was 1,435 mg in patients with abnormal proteinuria. The protein concentration was higher in 84 patients (76%) in the daytime urine and in 26 (24%) in the early morning urine ($P < 0.001$) and the mean protein concentration was markedly higher in the daytime urine (Table). The dipstick readings were higher in the daytime urine in 34 patients (31%) and in the early morning urine in 5 (4.5%) ($P < 0.001$) and were the same in 71 (64.5%). There were 23 (21%) negative readings in daytime urines and 30 (27%) in early morning urines. The latter included 1 patient excreting more than 1000 mg protein daily. Higher dipstick readings corresponded with higher protein concentration in the same urine in 35 of 39 samples (89%).

Discussion

It is often advised that early morning urine specimens should be screened for proteinuria as

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Table Urine Protein Concentration (mg/l) in Different Samples of Urine

Sample	*Normal patients*	*Patients with proteinuria*
Daytime random urine	76.5	1308
Early morning urine	70.1	828
Difference (SEM)	6.4 (±8.1)	480 (±84.7)
Confidence interval (5% level)	−9 9–22.9	312–648

they are more concentrated (Pryor, 1977; Raman and Lee, 1986). However, proteinuria may be increased by the upright position (King, 1957) and urine protein concentration is higher during ambulation even when adjusted for creatinine concentration (Ginsberg *et al.*, 1983).

This study shows that urine protein concentration not adjusted for creatinine concentration is usually higher in daytime samples than in early morning samples in patients with proteinuria, but there is no difference with normal subjects—perhaps because many patients with proteinuria do not concentrate the urine normally because of age, heart failure, renal failure or renal tubular defects. The study also demonstrates that pathological proteinuria is more likely to be detected when the daytime urine is tested with dipsticks, but heavy proteinuria is unlikely to be missed whichever sample is used. Testing daytime urine does not increase the false positive rate in normal subjects.

It is important not to miss abnormal proteinuria even when the protein excretion rate is below 1000 mg daily, since serious non-glomerular nephropathies need not cause heavy proteinuria. Persistent moderate proteinuria that is associated with azotaemia or with microscopic haematuria or that occurs between episodes of macroscopic haematuria suggests the presence of renal pathology. After dipstick testing, the accurate measurement of protein excretion may be achieved by the simultaneous measurement of protein and creatinine concentration in a single daytime urine sample (Ginsberg *et al.*, 1983; Shaw *et al.*, 1983).

We recommend that daytime samples of urine, not early morning samples, should be tested for protein.

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Case Reports

Scrotal Carcinoma Following Prolonged Use of Crude Coal Tar Ointment

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Case Report

A 67-year-old male with a 25-year history of generalised psoriasis presented with a 2-year history of a slowly enlarging scrotal lesion. He was a retired demolition worker with no history of exposure to recognised industrial carcinogens. Since 1981 he had been applying 10% crude coal tar ointment and Vioform Hydrocortisone 10% daily to his scrotal psoriasis.

On examination he had a raised, mobile, erythematous papule measuring 30 × 25 × 10 mm on the right side of his scrotal skin. The scrotal skin was generally blackened. An operative excision biopsy revealed a well differentiated, invasive, squamous cell carcinoma extending to a depth of 8 mm (Fig.).

Comment

Since the first description of "chimney sweep's disease" by Pott in 1775, the relationship of industrial exposure to carcinogens and the development of scrotal carcinoma has been well documented. The risk of carcinogenesis following the use of therapeutic crude coal tar preparations has been reported by Alexander and Macrosson (1954) and Moy *et al.* (1986) but is not widely appreciated.

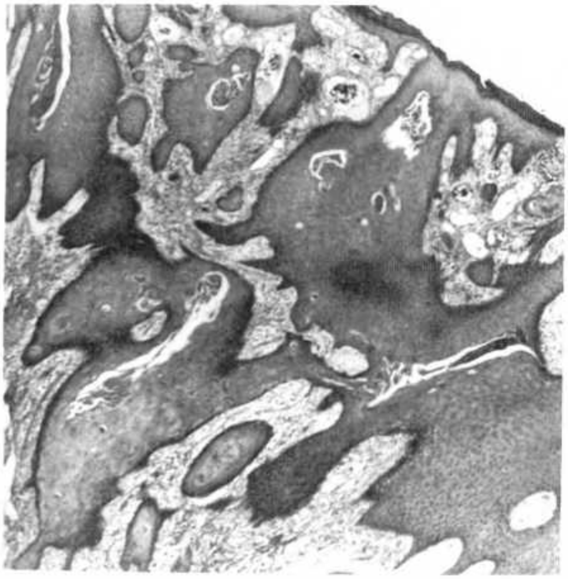

Fig. Section of invasive squamous carcinoma (H and E × 25).

Our patient had used a combination of crude coal tar and steroid ointment for 5 years before the development of carcinoma. Unlike other areas, the rugosity of scrotal skin is likely to increase the area in contact with the ointments and to prolong the length of time that the preparations are in contact with the skin, which may account for the relatively short carcinogenic induction time in this patient. A history of prolonged use of coal tar ointments should be sought in patients presenting with suspicious lesions of the scrotal skin.

Acknowledgements

I thank the following for their help in preparing this report: Mr I. F. Kerr, Dr R. S. Chapman, Dr G. Smith and Mrs M. McDougall (Stobhill Hospital) and the Departments of Medical Illustration and Pathology (Monklands District General Hospital).

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Retrovesical Echinococcal Cyst

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Case Report

A 25-year-old man presented with a 1½-year history of frequency and poor stream. Palpation revealed a large hypogastic mass which was confirmed by rectal examination. IVU showed bladder compression (Fig.) and ultrasound revealed a cystic mass behind the bladder. No other fluid collections were found. At laparotomy the cyst was removed through the posterior peritoneum and the

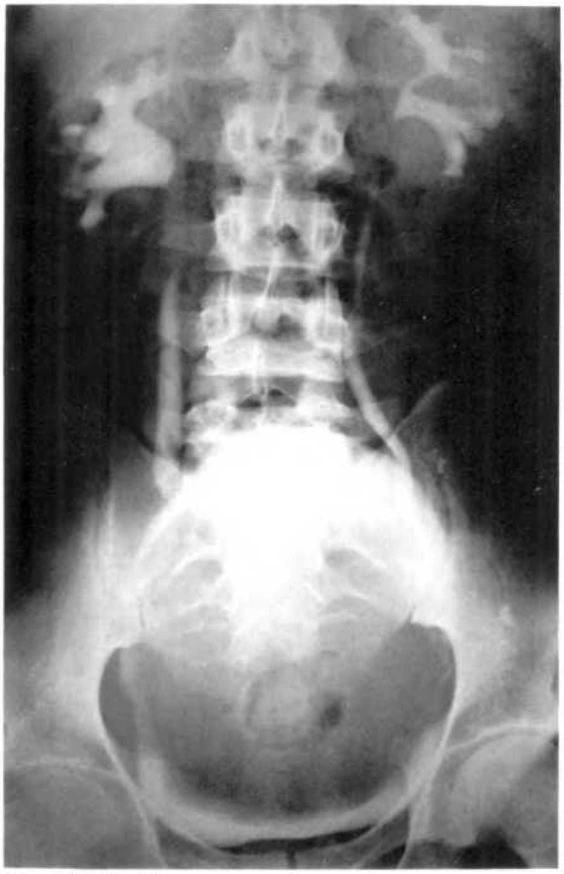

Fig. IVU (bladder compression).

patient's post-operative course was uneventful. He remains well 10 months later.

Comment

Retrovesical echinococcal cysts are uncommon (Amar *et al.*, 1983). In Tunisia, where hydatid disease is endemic, less than 10 have been reported, whereas about 100 renal cysts have been encountered since the 1970s. The kidney is the location in 4% of all treated echinococcal cysts.

The diagnosis of these cysts has been helped by modern imaging techniques and they usually appear as a fluid collection with septa (Gharbi *et al.*, 1981). Treatment consists of removal of the whole cyst and most of the surrounding hyalin tissue.

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Autoimmune Thrombocytopenia in Renal Carcinoma

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Case Report

A 68-year-old woman was admitted with haematuria and bruising. A left renal mass extended to the umbilicus. Peripheral blood values showed haemoglobin 8.4g%, white cell count 6.8×10^9/l and platelet count of 7×10^9/l. Ultrasound confirmed an 18-cm tumour in the left kidney. Liver function tests, prothrombin time and partial thromboplastin time were normal. Bone marrow biopsy was normocellular, with abundant megakaryocytes. The aspirate showed numbers of young, agranular megakaryocytes with absent platelet budding. Infusion of platelet concentrates failed to raise the platelet count.

Splenectomy and radical nephrectomy were carried out under platelet transfusion cover. The platelet count 2 h post-operatively was 202×10^9/l. Histology of the renal mass showed renal carcinoma and that of the spleen showed mild splenic congestion.

The patient remains well 20 weeks post-operatively, with a recent platelet count of 589×10^9/l.

Comment

Autoimmune thrombocytopenia is known to be associated with lymphoproliferative disorders (Kaden *et al.*, 1979) and has also been reported, less commonly, in association with solid tumours (Schwartz *et al.*, 1982). It has been described in a patient with renal carcinoma but was directly related to interferon therapy (Abdi *et al.*, 1986).

We report a case of simultaneous presentation of renal carcinoma and thrombocytopenia. That the thrombocytopenia was immune-mediated is supported by the marrow aspirate megakaryocyte morphology, bone biopsy showing increased numbers of megakaryocytes, failure to achieve a rise in numbers following platelet transfusion, and the rapid response to splenectomy. Unfortunately, antiplatelet antibodies were not assayed, but there was no evidence of other causes of thrombocytopenia such as drug ingestion, bone marrow hypoplasia or disseminated intravascular coagulation.

The phenomenon of autoimmune-mediated thrombocytopenia should be recognised because it has important therapeutic implications, as demonstrated by our patient's response to splenectomy.

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Emphysematous Pyelonephritis: Diagnosis by Ultrasound

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Renal ultrasonography in emphysematous pyelonephritis has been deprecated and is often overlooked as a diagnostic tool. Its use in the present case is discussed.

Case Report

A 64-year-old, previously undiagnosed diabetic woman was admitted in septic shock. Blood cultures grew *Escherichia coli*. Renal ultrasound showed high intensity echoes with acoustic shadowing arising within the renal sinuses and perinephric space. An area of mixed echoes within the lower pole had an appearance similar to that of bowel gas (Fig.). Plain X-ray showed gas in the bladder and right renal pelvis and a streak of gas in the perinephric space. Computed tomography (CT) added no additional information. On these findings the diagnosis of emphysematous pyelonephritis with a localised lower pole abscess was made.

After commencement of insulin and intravenous antibiotics the initial surgical treatment was open drainage of the perinephric space and the lower pole abscess. The patient improved clinically, but recurrence of fever and persistent *Escherichia coli* urinary infection necessitated nephrectomy. This was followed by a rapid recovery.

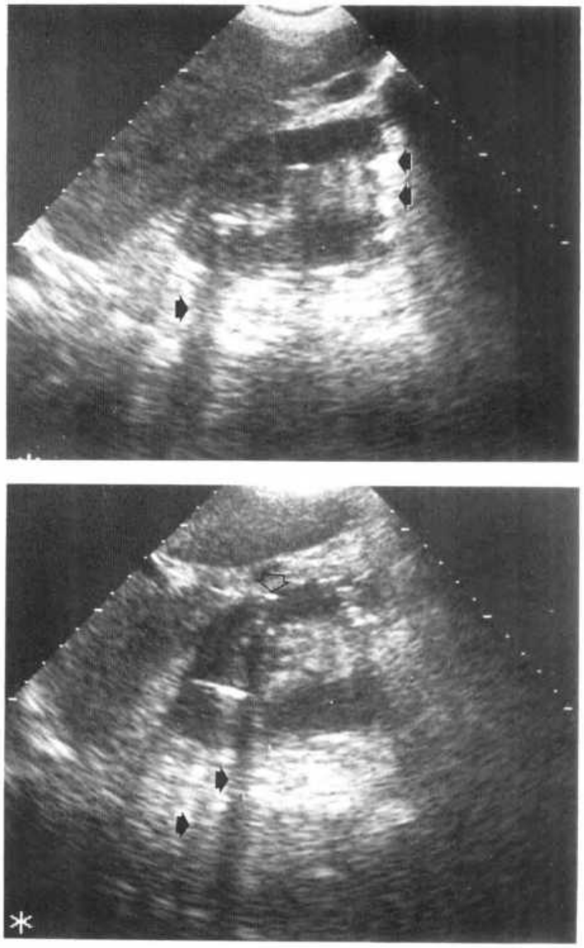

Fig. The enlarged right kidney is seen below the liver. ▲ Gas in lower pole abscess. ▼ Acoustic shadowing. ⇨ Gas echoes in perinephric space.

Comment

The use of plain radiography and CT scanning is well described in the diagnosis of emphysematous pyelonephritis (Michaeli *et al.*, 1984; Hudson *et al.*, 1986). Non-function of the affected kidney often renders intravenous urography of limited use (Michaeli *et al.*, 1984). However, the role of ultrasound has been deprecated (Ahlering *et al.*, 1985).

Gas produces strong echoes on ultrasound and the widespread echoes in the renal pelvis, renal parenchyma and perinephric space were diagnostic in this case (Fig.). Plain film radiography was essential to exclude stones, which also cause prominent echoes.

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Testicular and Epididymal Histology in a Fetus with Klinefelter's Syndrome at 22 Weeks' Gestation

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Case Report

A woman who underwent a diagnostic amniocentesis elected to have a therapeutic termination of pregnancy when the karyotype of the male fetus showed the chromosomal anomaly of 47,XXY, otherwise known as Klinefelter's syndrome. Following an abortion induced by an intra-uterine infusion of prostaglandins, the gonads were examined both macroscopically and histologically.

The testes were intra-abdominal. The testes and their epididymal appendages were excised and fixed in Bouin's solution followed by a 70% solution of ethyl alcohol. The tissues were then processed in the usual way and after wax mounting, sections 5 µm in thickness were cut and stained using a modification of the Gomori trichrome stain.

Histology of both the testes and the epididymides showed no abnormality. Examination of both gonads revealed entirely normal fetal testicular tissue. There was no evidence of the tubular atrophy, the tubular hyalinisation or the Leydig cell hyperplasia seen in the adult testis of a patient with Klinefelter's syndrome (Fig. 1). The epididymal tubules were also normal and the cilia were easily visible within their lumina (Fig. 2).

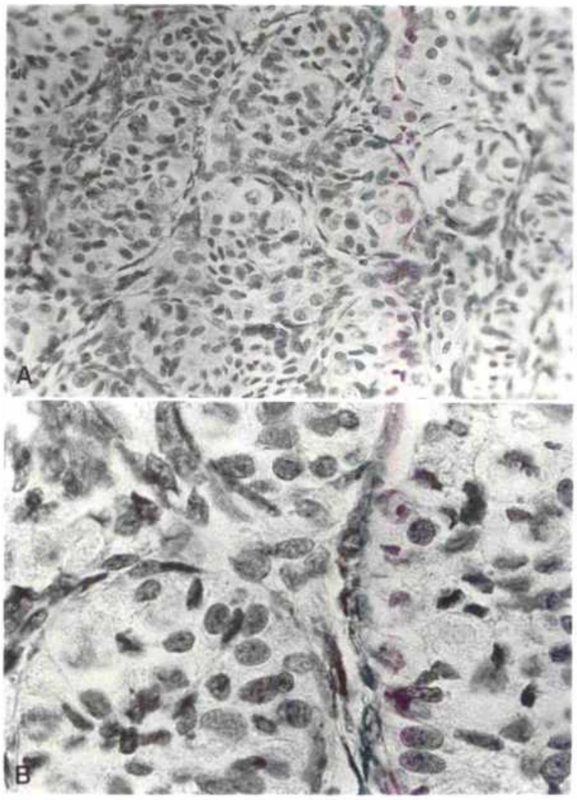

Fig. 1 Histological sections A (× 250) and B (× 1000) of a testis taken from a 22-week fetus known to have a white cell karyotype of 47,XXY. The testicular tissue shows a normal tubular architecture and normal numbers of spermatogonia. The Leydig cell numbers also appear normal.

Comment

Klinefelter's syndrome is very difficult to diagnose at birth as the testes are usually descended and are of normal size (Harris and Heller, 1974). Testicular lesions are known to occur in childhood and more especially in the pre-pubertal period (Ferguson-Smith, 1959). However, when these changes are initiated in the testes is not clear. In 1982, Rock *et al.* showed the presence of normal histology in a fetus aborted at 16 weeks' gestation. The case presented here also demonstrated normal histology of both the testes and the epididymides. It shows that not only does the testicular histology remain undisturbed into the second half of intra-uterine life but in view of the normal epididymal morphology, so does testicular function, at least in terms of testosterone production. The functional and structural abnormalities associated with Klinefelter's syndrome do not occur during the development or the differentiation of the fetal testis.

Acknowledgement

We wish to thank Mr A. J. Tyack, Consultant Obstetrician at the City Hospital, Nottingham, for permission to report on the fetus from one of his patients.

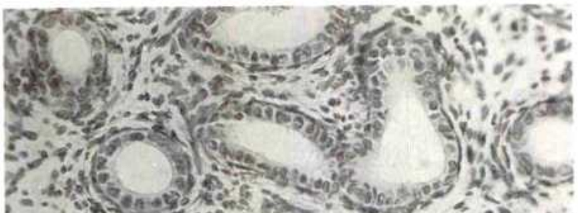

Fig. 2 Histological sections A (× 250) and B (× 1000) of an epididymis taken from the same fetus. The epididymal architecture is also normal and the cilia present on the tubular epithelium are clearly visible.

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Bilateral Testicular Atrophy following Blunt Trauma

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Serious trauma to the scrotum and testis is not commonly seen, although unilateral testicular rupture is being reported more often (McAninch *et al.*, 1984) and a few cases of unilateral testicular dislocation have been reported (Goulding, 1976). However, bilateral testicular injury is rarely seen (Bernardi and Agugliaro, 1959; Neistadt, 1967). We report a case of bilateral testicular atrophy following blunt scrotal trauma.

Case Report

A 27-year-old man was admitted to hospital after the car under which he was working had fallen off its supports on to him. A revolving wheel landed on his pelvis. On assessment he was found to have a fractured pelvis and a degloving injury of the scrotum and base of penis, most extensive on the right side. Examination under general anaesthesia showed that the right testis had completely prolapsed through the anterior scrotal wall and the left anterior scrotum was degloved down to the tunica vaginalis. Neither tunica albuginea had been breached and both testes appeared completely viable. Fresh bleeding was obtained through a short incision made in the tunica albuginea of the right testis.

The scrotum was refashioned about both testes and primary closure of the entire injury obtained. The postoperative course was uneventful and excellent healing resulted.

At review 5 months later the patient complained that he had gradually become aware of a decrease in sexual potency and for the past 4 weeks had ceased to obtain penile erections or ejaculation. On examination both testes were found to have atrophied to pea-sized nodules. Serum testosterone was at castrate levels of 1.5 nmol/l. Serum FSH was 66.2 u/l and serum LH 63.4 u/l, both markedly elevated, indicating testicular failure. Initial treatment with mesterolone produced only transient symptomatic and biochemical improvement. The patient now enjoys normal sexual activity on 3-monthly testosterone implants, though he is, of course, azoospermic.

Comment

We have previously described testicular atrophy following apparently successful repair of testicular rupture (MacDermott *et al.*, 1988). In this case there was neither rupture of the tunica albuginea nor disruption of the macroscopic blood supply of either testis; indeed the testes appeared completely viable at operation. The testes and scrotum were, however, caught under the revolving car wheel and subjected to a compressive force. This would have been sufficient to cause microvascular damage to the testicular tissue leading to atrophy. This case again illustrates the importance of microstructural damage in testicular trauma.

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Autotransplantation of the Vermiform Appendix following Ureteroscopic Damage to the Right Ureter

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Case Report

A 38-year-old man with right renal colic was admitted for ureteroscopic removal of the calculus on account of persisting symptoms and associated obstruction (Fig. 1). At cystoscopy the right ureteric orifice was hydrostatically dilated and a rigid ureteroscope was passed. The stone was visualised and snared, using a Dormia basket, prior to ultrasonic destruction. Extraction failed and the basket became trapped, necessitating open exploration. The stone and basket were removed but the ureter at that point had been avulsed and required repair with an end-to-end anastomosis over a double J ureteric stent. Initial post-operative recovery was satisfactory but after 7 days a urinary fistula developed. The ureter was re-explored and complete necrosis was found at the site of the previous injury. The vermiform appendix was mobilised on its vascular pedicle, irrigated with normal saline and anastomosed end-to-end with the ureter over a double J ureteric stent to repair the defect. There remained a continual leak of urine from the operative site. Urography demonstrated displacement of the stent through the upper anastomosis and it was therefore repositioned. The urine leak subsided and the patient was discharged with the stent *in situ*; 3 months later this was removed endoscopically. Subsequent urography demonstrated satisfactory ureteric substitution (Fig. 2).

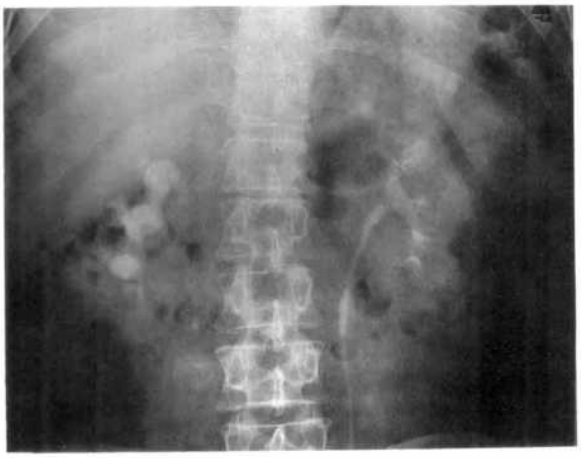

Fig. 1 Intravenous urogram demonstrating right ureteric calculus with proximal pelvicaliceal obstruction.

Comment

Ureteric damage following ureteroscopic manipulation using the Dormia basket is well recognised (Kaufman, 1984). Chatelain (1979) described a method of repair using the vermiform appendix. We recommend that calculi below the pelvic brim be extracted ureteroscopically; because of the greater risk of damage, however, those above the

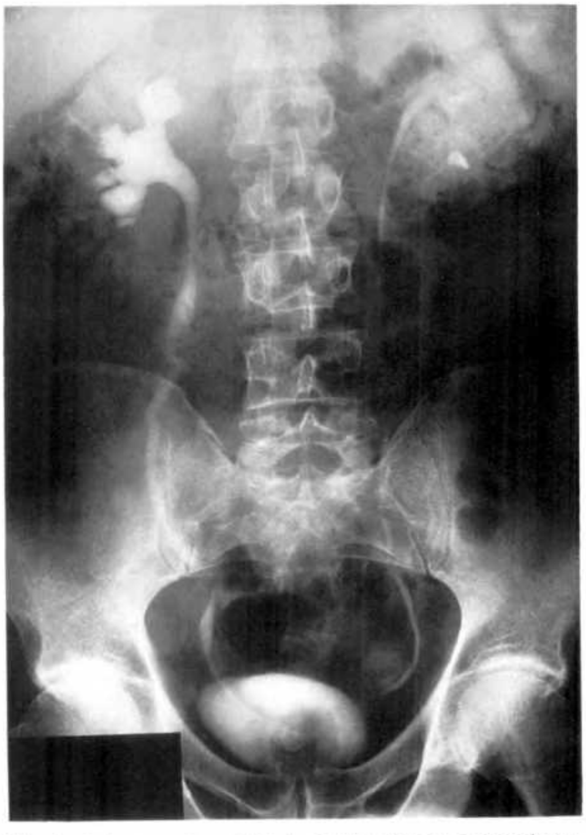

Fig. 2 Intravenous urogram 3 months after autotransplantation, showing vermiform appendix *in situ* replacing damaged middle portion of right ureter.

pelvic brim should be manipulated back into the renal pelvis and treated with either percutaneous nephrolithotomy or extracorporeal shockwave litholotripsy as suggested by Payne *et al.* (1985).

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Duplication of the Upper and Lower Urinary Tract

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Approximately 40 cases involving a double bladder have been reported in the literature, but none with the clinical picture reported here (Esham and Homer, 1980). According to Abrahamson (1961), 87% of these patients also had duplication of the genital tract, 56% had some form of intestinal tract duplication and 12% had duplication of the spine. The double bladder anomaly is often diagnosed in early infancy. In a few cases the diagnosis is made incidentally in adult patients.

Case Report

A 75-year-old woman was admitted with lower abdominal pain, fever and leucocytosis. Gynaecological examination revealed a 10 × 10 cm cystic tumour in the pelvic cavity. No residual urine was found and both cystoscopy and intravenous urography were normal. On the fifth day about 1 litre of thin, greyish pus was discharged from the vagina. The cystic tumour was no longer found but in the midline of the anterior wall of the vagina a fistulous opening was seen from which pus could be expressed. After a few days only small amounts of clear urine were secreted.

Fistulography combined with intravenous urography revealed a completely separate extra bladder with its own dilated and tortuous ectopic ureter ending up in a small round cavity (Fig.).

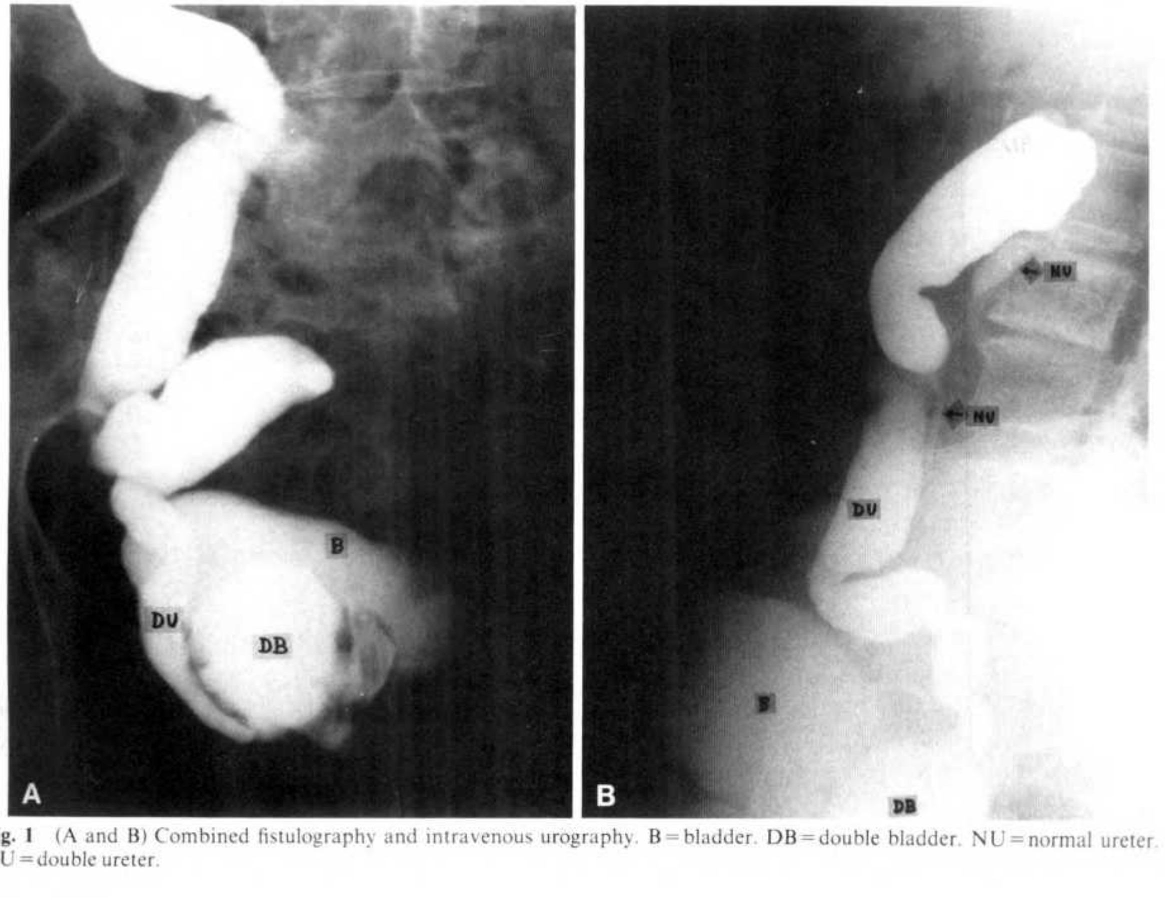

Fig. 1 (A and B) Combined fistulography and intravenous urography. B = bladder. DB = double bladder. NU = normal ureter. DU = double ureter.

A review of the patient's history revealed that since infancy she had suffered from drip incontinence, which 2 years earlier had led to an anterior colporrhaphy with good effect on the incontinence.

Comment

Duplication of the bladder is an extremely rare condition and the embryological basis is largely unknown (Abrahamson, 1961; Woodhouse and Williams, 1979). In the present case two different developmental anomalies may have occurred. At the earlier operation for incontinence the ectopic urethra was not diagnosed and was oversewn, leading to stasis and infection in the extra urinary tract.

The usual treatment is extirpation of the entire extra urinary tract or anastomosis of the two bladders (Woodhouse and Williams, 1979). However, in the present case, because of the patient's advanced age and her relatively minor discomfort, no surgery was performed. Although a double bladder and urethra are rare, they should be considered in cases of incontinence.

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Haematuria due to Mucocele of the Appendix

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Case Report

A 51-year-old man was referred with a 36-h history of haematuria. Although this was painless initially, he experienced pain in the right iliac fossa between initial presentation and his out-patient appointment 2 weeks later.

On examination there was a cough impulse in the right groin but no other physical signs were elicited. Plain abdominal X-ray showed a partially calcified mass in the right iliac fossa (Fig. 1) and on the intravenous urogram there was a partial obstruction of the right ureter at that level (Fig. 2). Computed tomography (CT) demonstrated that the lesion was predominantly cystic and closely related to the caecum and ureter and extended into the pelvis between the bladder and the rectum (Fig. 3).

At cystoscopy the bladder appeared normal and a ureteric catheter was passed easily up the right ureter. Laparotomy revealed a calcified mucocele of the appendix, secondary to a polypoid mass within the caecum. The mucocele was excised and right hemicolectomy performed. Histology of the caecal lesion was that of a carcinoid tumour.

The patient made a rapid and complete recovery.

Comment

Mucoceles of the appendix develop as a result of obstruction of the proximal lumen of the organ (Kalmon and Winningham, 1954) and are an exceedingly rare presentation of colonic tumours (Hilsabeck *et al.*, 1952). Although ureteric compression due to a mucocele has been previously described (Bonnan and Davis, 1948), this is the first report of an appendicular mucocele presenting with haematuria. With the benefit of hindsight the CT scan appearances are diagnostic. The case illustrates the importance of careful assessment of the caecum to exclude underlying pathology when a mucocele of the appendix is excised.

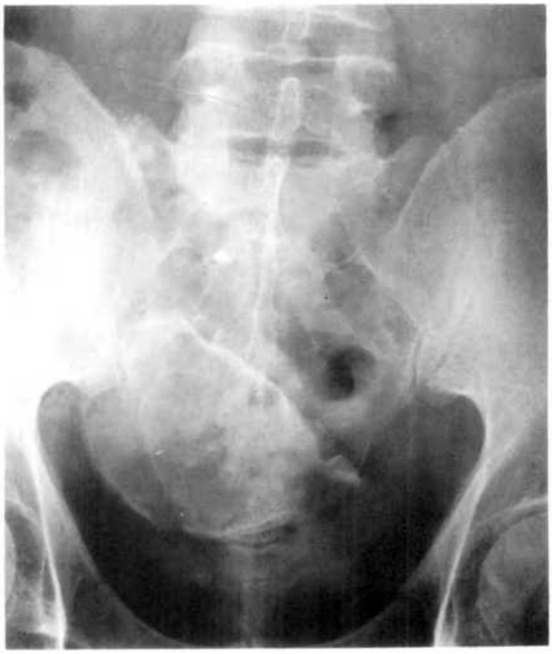

Fig. 1 Plain abdominal X-ray showing a partially calcified mass in the pelvis.

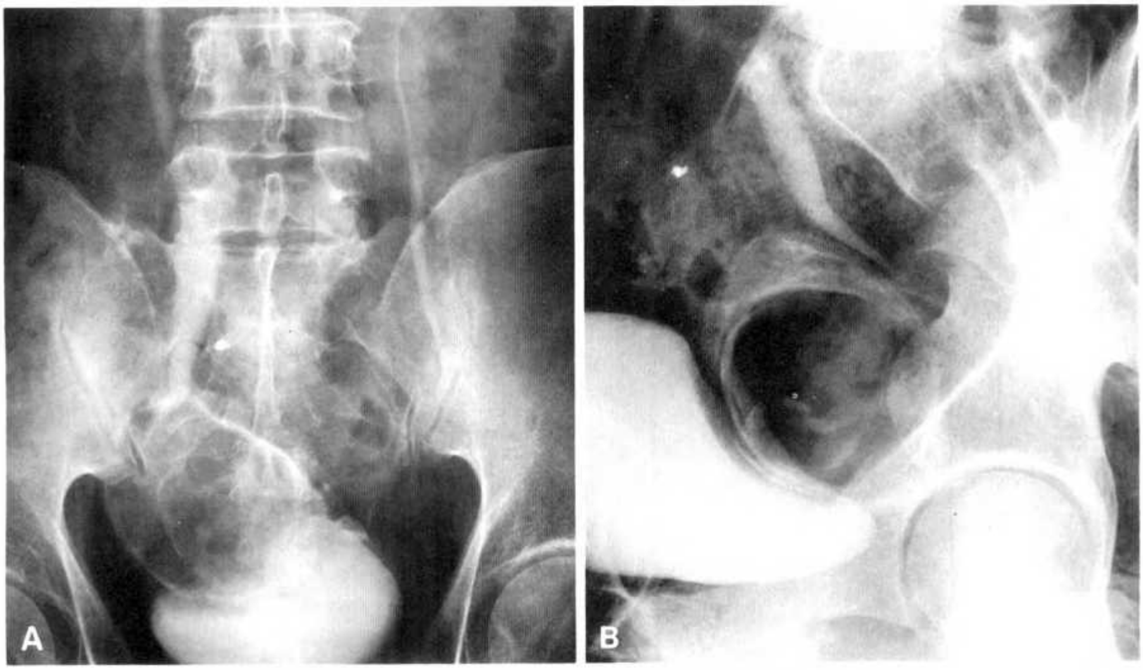

Fig. 2 (A and B) IVU showing partial obstruction to the right ureter caused by the mass.

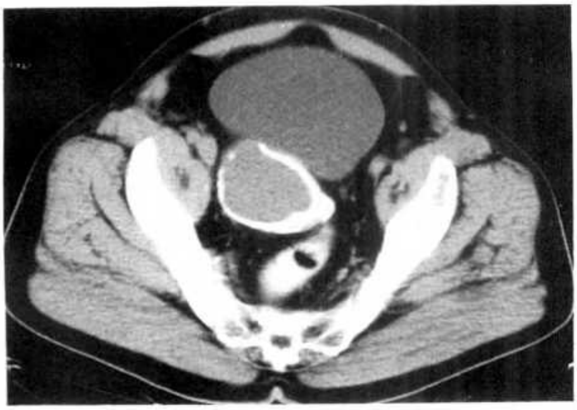

Fig. 3 CT scan of the pelvis showing a thick walled, fluid filled, partially calcified structure lying behind the bladder and in front of the rectum.

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Requests for reprints to: R.S. Kirby, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Point of Technique

Elevation of the Vagina during Colposuspension: the Use of a Deaver Retractor

B. T. HAYLEN, M. I. FRAZER, D. GOLOVSKY and R. J. F. McINERNEY, *Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, Liverpool*

The practice of pushing up the paraurethral vaginal tissue during a Burch colposuspension aids the dissection of the bladder off the vagina. It also allows an assessment of the degree of possible elevation prior to placement of sutures. The standard operative technique involves the use of the fingers of either the surgeon or the assistant to press up, paraurethrally, on the anterior vaginal wall (Burch, 1961). This often results in difficulty since the fingers of most people are neither long enough to achieve optimum elevation nor strong enough to endure a long and difficult dissection. Needlestick injuries to either the surgeon's or assistant's fingers are also an ever-present danger.

We advocate the use of a narrow (3-cm) Deaver retractor in order to overcome these problems (Fig.). The end of the retractor is inserted vaginally by the surgeon and positioned against the anterior vaginal wall, in turn on each side of the urethra. Initially, the retractor should be angled well laterally. The position is then maintained by the assistant.

There are several advantages to this technique. It allows good bites to be taken of vaginal tissue since sutures are not being manoeuvred around gloved fingers. It also prevents the operator's or assistant's glove from being inadvertently sutured to the anterior vaginal wall. It avoids needlestick injuries and consequently lessens the risk of acquiring infectious disease. It eliminates "finger fatigue" to either assistant or surgeon, especially if the dissection is difficult. In many cases it can allow a superior assessment of the potential vaginal elevation because the retractor is longer than most fingers. Because of the easier dissection, the procedure tends to be quicker and bleeding is reduced; the anatomical result is at least as good. A greater degree of asepsis is possible since neither the surgeon's nor the assistant's fingers need enter the vagina. An experienced assistant to tie the knots is no longer necessary because the surgeon's own fingers are not committed to elevating the vagina.

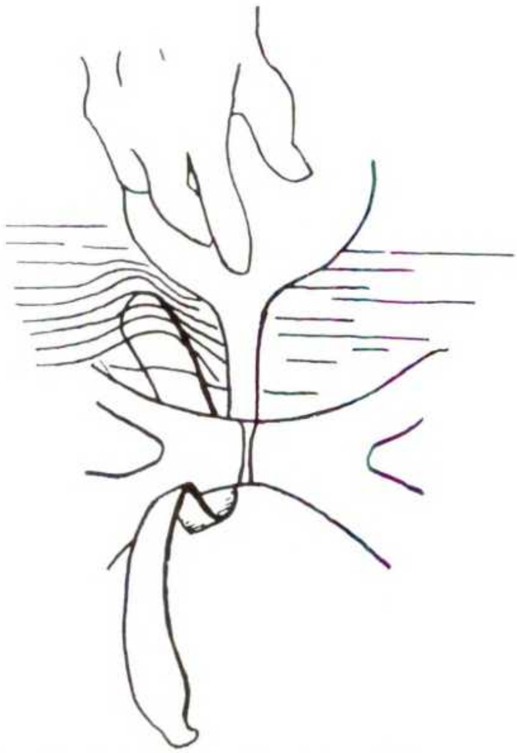

Fig. Elevation of vagina during colposuspension.

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

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An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

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Silver Jubilee British Congress of Obstetrics and Gynaecology

Queen Elizabeth II Conference Centre, London. 4–7 July 1989

Further information from: Caroline Roney, Congress Organiser, Congress House, 65 West Drive, Sutton, Surrey SM2 7NB.

Urological Society of Australasia. 42nd Annual Meeting

Melbourne, Australia. 2–7 March 1989

Further information from: Secretary, Urological Society of Australasia, 145 Macquarie Street, Sydney, NSW 2000, Australia.

International Symposium on Dysfunction of the Lower Urinary Tract: Present Achievements and Future Perspectives

Nijmegen, The Netherlands. 3–4 March 1989

Further information from: Miss Marion van Beckhoven, c/o Department of Urology, Radboud University Hospital, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Ghent's Urethral Surgery Day

Ghent, Belgium. 14 April 1989

Live demonstrations will be given of urethral reconstructive surgery (hypospadias, strictures, etc).

Further information from: Professor W. A. De Sy, Department of Urology, University Hospital, 9000 Ghent, Belgium.

Seventh International Symposium of Radionuclides in Nephro-urology

Williamsburg, USA. 7–10 May 1989

Topics for discussion include hypertension, renal physiology, radiopharmaceuticals, renal function, renal imaging, metabolic disease, transplantation, paediatrics and urological diseases.

Further particulars from: Dr M. Donald Blaufox, Department of Nuclear Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.

54th Congress of the Belgian Society of Urology

Brussels, Belgium. 27–28 May 1989

The topic will be "Lower Urinary and Genital Pathology in Children."

Further particulars from: Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.

XVIIIth Annual Conference of the European Dialysis and Transplant Nurses Association—European Renal Care Association

Göteborg, Sweden. 11–14 June 1989

XXVIth Congress of the European Dialysis and Transplant Association—European Renal Association

Göteborg, Sweden. 11–15 June 1989

Further information from: General and Scientific Secretariat, Transplant Unit, Department of Surgery, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

Canadian Urological Association

Quebec City, Canada. 18–22 June 1989

Further information from: Dr J. P. Collins, B–3, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.

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REVIEW

Peyronie's Disease

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Even though he was not the first to describe it, the name of Francois Gigot de la Peyronie, Surgeon to Louis XV of France, has become synonymous with this rather enigmatic though not uncommon condition. The disease is characterised by the appearence of irregular dense plaques of fibrous tissue, usually on the dorsum of the penile shaft, accompanied by distortion or angulation of the erect penis and, in the early stages, pain on erection. The condition is readily differentiated from congenital curvature of the penis with or without chordee but the plaque may mimic, albeit rarely, a more sinister condition such as an epithelioid sarcoma of the penis (Moore *et al.*, 1975). Peyronie's disease may cause sexual dysfunction in various ways. The erectile deformity itself may interfere with vaginal penetration or make coitus uncomfortable. The plaque, if large and associated with fibrosis of the underlying cavernosal erectile tissues, may result in a band-like constriction or waisting of the penile shaft, leading to flaccidity of the corpora distal to this. Alteration of the normal properties of the tunica albuginea by extensive fibrosis appears also to lower the axial rigidity of the erect penis, thus causing it to buckle more easily during attempted penetration (Desai *et al.*, unpublished observations). Failure of erection in men with Peyronie's disease is usually psychogenic in nature, secondary either to performance anxiety or to spectatoring, but may also be due to coexistent penile arterial insufficiency, especially in the elderly patient. In diabetic men, neurological as well as vascular factors may be relevant. A further pathophysiological mechanism that has been thought to contribute to loss of erectile rigidity in Peyronie's disease is cavernosal venous leakage through areas of tunical involvement (Metz *et al.*, 1983).

Although the clinical features are well recognised and have been well documented (Chesney, 1975; Bystrom and Rubio, 1976; Chilton *et al.*, 1982), the aetiology of this condition remains obscure. Histopathological studies (Smith, 1966; Vande Berg *et al.*, 1981) have suggested that the disease process commences as a vasculitis, with chronic inflammatory cellular cuffing and endothelial proliferation affecting the small vessels within the areolar connective tissue layer between the tunica albuginea and the cavernosal sinusoids. This later progresses to fibrosis, which may encroach upon and involve the erectile tissue (Pugh, 1960), and also to calcification in a variable proportion of patients (Bystrom and Rubio, 1976; Vande Berg *et al.*, 1982; Gelbard, 1988). Amidst the plethora of speculation that currently exists regarding the aetiology, a plausible theory is that Peyronie's disease represents a manifestation of an inherent (? autoimmune) tendency to an exaggerated though localised fibrotic response to a mechanical stress injury of the tunica albuginea (Hinman, 1980) which need not necessarily be overt in nature. Plaque-derived cell cultures have confirmed this enhanced fibroproliferative capacity when compared to penile cell cultures derived from adjacent normal tunica (Somers *et al.*, 1982).

The natural history of the disease process cannot be predicted in an individual patient at the time of presentation. Although the pain almost always subsides spontaneously within a few months of onset, the outcome with regard to the plaque, and hence the degree of angulation on erection, is much less certain. Williams and Thomas (1970) reported the fate of 12 such patients left untreated for up to 8 years and noted spontaneous resolution of the plaque in 6, in 4 of whom it was accompanied by straightening of the penis. The mean interval to complete resolution was 4 years. Ashworth (1960), on the other hand, found that none of his 8 untreated patients, observed for up to 5 years, regained

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normal sexual function; in 1 man the degree of fibrosis worsened and though the plaques either disappeared or became smaller in 4 other patients, this was at the expense of sexual potency. However, one must be cautious in interpreting these somewhat anecdotal reports and if reliable prognostic criteria are to be defined, large-scale prospective studies of the natural history of this condition will be required. These will, of necessity, have to be multicentred because the disease is not encountered frequently enough in any one centre. At present, therefore, all one can say is that the degree of angulation on erection may be expected to improve in some, stay the same in most and perhaps worsen in others. The plaques may or may not undergo resolution and indeed may even migrate from the original location. Owing to the uncertainty about the eventual outcome it is important to explain this to the patient as well as the nature of the underlying pathology, emphasising the need for patience in order to assess the evolution of the condition in his particular case. Because of the variable degree of progression or regression that may ensue naturally, it is not difficult to appreciate that the value of the various medications used in the initial acute phase is difficult to evaluate. Thus the therapeutic merits of vitamin E either alone (Scardino *et al.*, 1949) or in combination with steroids (Bystrom and Rubio, 1976), procarbazine (Aboulker and Benassayag, 1970; Morgan and Pryor, 1978), potaba (Zarafonetis and Horrax, 1959; Shah *et al.*, 1983) and orgotein (Bartsch *et al.*, 1981; Gustafson *et al.*, 1981) remain questionable. Similarly, there is no convincing evidence that either radiotherapy (Furlow *et al.*, 1975; Landthaler *et al.*, 1983; Carson and Coughlin, 1985) or the application of ultrasound (Heslop *et al.*, 1967) influences the course of the disease apart from perhaps hastening the resolution of pain. This also seems to be the main value of steroids injected directly into the plaque (Desanctis and Fury, 1967; Winter and Khanna, 1975). Whilst encouraging preliminary results have been reported from California with the injection of purified clostridial collagenase into the plaque (Gelbard *et al.*, 1985), further work is still required to resolve the problems of optimum dosage, and the potential for developing dangerous anaphylactic reactions following repeated treatment remains a worry. As yet the preparation is neither available nor licensed for use in the United Kingdom.

If any valid study of Peyronie's disease and its progress is to be undertaken, then more sophisticated methods of assessing the dimensions of the plaque and the degree of angulation on erection will have to be invoked. These are now available. Plaque size can be accurately measured and the presence or absence of calcification determined using high resolution ultrasonography (Fleischer and Rhamy, 1981; Hamm *et al.*, 1986) and subsequently any change monitored. The extent of fibrotic encroachment on the cavernosal erectile tissue can be determined by means of cavernosography (Hamilton and Swann, 1967; Bystrom *et al.*, 1974), CT scanning (Rollandi *et al.*, 1985) or even NMR imaging (Bellerofonte *et al.*, 1987) of the erect penis. The erectile deformity can be documented by polaroid photography, either at home (Kelami, 1983a) or in the out-patient clinic by inducing an erection with an intracavernosal injection of a vasoactive drug such as papaverine (Desai and Gingell, 1987). The papaverine test, by rendering the penis tumescent, also facilitates not only the delineation of the extent of plaque and any areas of corporeal fibrosis but also the detection of distal flaccidity. Moreover, if potency is in question, the integrity of the penile arterial inflow can be simultaneously evaluated by dynamic Doppler studies (Desai *et al.*, 1987). In this context it is worth noting that the routine pharmacological induction of erections as a diagnostic procedure in patients complaining primarily of impotence may reveal coexistent asymptomatic Peyronie's disease in some. In a personal series of 126 patients evaluated for erectile dysfunction between 1986 and 1987, we encountered 9 such instances, 6 of whom were diabetic and 3 who had significant penile arterial insufficiency (Desai and Gingell, unpublished observations).

Despite the controversy that still exists regarding the early management of Peyronie's disease, the role of surgical intervention is more clearly defined. If the patient is still potent but unable to achieve penetration because of the severity of curvature, the penis can be straightened. The operation devised originally by Nesbit (1965) for correcting congenital curvature of the penis has been increasingly applied to correcting the erectile deformity caused by Peyronie's disease (Pryor and Fitzpatrick, 1979; Lemberger *et al.*, 1984; Bailey *et al.*, 1985). In this operation single or multiple ellipses or diamond-shaped segments of normal tunica albuginea are excised from the corpora, opposite the point of maximum curvature, which when sutured straighten the penis, albeit at the expense of length. This is much simpler, less time-consuming and more predictable in achieving a satisfactory result than attempts at excising the often extensive plaques and replacing the resultant defects with either a dermal graft (Bystrom *et al.*, 1973; Devine and Horton, 1974) or other substitutes including lyophilised dura (Kelami, 1977), tunica vaginalis (Das, 1980), Dacron (Lowe *et al.*, 1982) or silastic (Yeates, 1988). For optimum results with the Nesbit procedure, the disease should have been present for at least a year and stable for at least 3 months. If the patient is impotent and relevant objective tests have confirmed this to be of predominantly organic aetiology, the insertion of semi-rigid penile prostheses is an acceptable procedure with or without excision or incision of the plaques (Raz *et al.*, 1977; Kelami, 1983b; Subrini, 1984). With the advent of self-injection programmes using vasoactive agents (Zorgniotti and Lefleur, 1985) surgical straightening of the penis by a Nesbit operation and subsequent restoration of erectile function by intracavernosal papaverine injection offers a potentially more physiological method of achieving vaginal penetration than the insertion of penile prostheses. This approach, however, should be applied with caution as the long-term side effects of repeated injections into the penis remain to be determined, especially with regard to cavernosal fibrosis which has been reported, though rarely (Desai and Gingell, 1988). In those patients with psychogenically induced impotence, self-injection after a Nesbit's procedure may be required on a short-term basis only.

In conclusion, while much needs to be unravelled about this curious condition, there is no reason why it should signal an end to the sexual life of any man afflicted by it. For those not responding to conservative measures or demonstrating spontaneous improvement, effective surgical treatment can now be offered if the patient is sufficiently well motivated.

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Hyperthermia with Simultaneous Administration of Interferon Using Established Human Renal Carcinoma Heterotransplanted in Nude Mice

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Summary—Using human renal carcinoma heterotransplanted in nude mice, the effects of the combined use of hyperthermia and interferon (natural human interferon-alpha; IFN-alpha, and recombinant interferon-gamma; IFN-gamma) were examined. The hyperthermic device used was the Clini-Therm, Mark VII, 915 MHz, microwave. The administration of interferon was started immediately before hyperthermia and carried out on consecutive days. The combined use of hyperthermia and IFN was compared with hyperthermia and with IFN alone. The combined use of hyperthermia and IFN-alpha was shown to have significant anti-tumour effects compared with the former or latter alone. Of 10 nude mice (10 implanted tumours) used for the experiment, 5 showed complete disappearance of the implanted tumours and the others showed prolongation of survival. Combined treatment with IFN-gamma and hyperthermia showed no significant effect when compared with other treatment groups. Combined treatment with local hyperthermia and IFN-alpha may have some application to the clinical management of renal carcinoma.

Hyperthermia is the application of heat as an anti-cancer treatment. This approach has aroused interest because, during the last 5 or 6 years, it has proved effective against cancers which were considered refractory. However, hyperthermia treatment alone does not give satisfactory results and in order to develop an additional multidisciplinary approach to the treatment of various cancers, we investigated the concurrent use of auxiliary therapy. The application of hyperthermia to renal carcinoma remains virtually unexplored and no basic research has been conducted. At the same time, interferons have been found to be ineffective when used alone and a search is being made for effective simultaneous auxiliary therapy. We report the results of a study of hyperthermia with the concurrent administration of IFN, using human renal carcinoma heterotransplanted in nude mice.

Material and Methods

BALB/C nu+/nu+ male mice aged 6 to 8 weeks were used.

The human renal carcinoma (JRC11), used in the present study, was established at a hospital affiliated to the Jikei University School of Medicine from the isolated tumour cells obtained from surgical specimens and was undergoing maintenance subcultivation. Structurally, the histological type of this implantable tumour exhibits an anaplastic pattern and it is of the spindle cell type. The tumour doubling time is as little as 2.72 days, indicating that it is a rapidly growing carcinomatous cell (Fig. 1).

The hyperthermic device was manufactured by Clini-Therm Co. Ltd. The core of the tumour was subjected to 915 MHz microwave hyperthermic treatment by means of an antenna inserted via a 16-gauge puncturing catheter which was connected with a Mark VII generator. The temperature was

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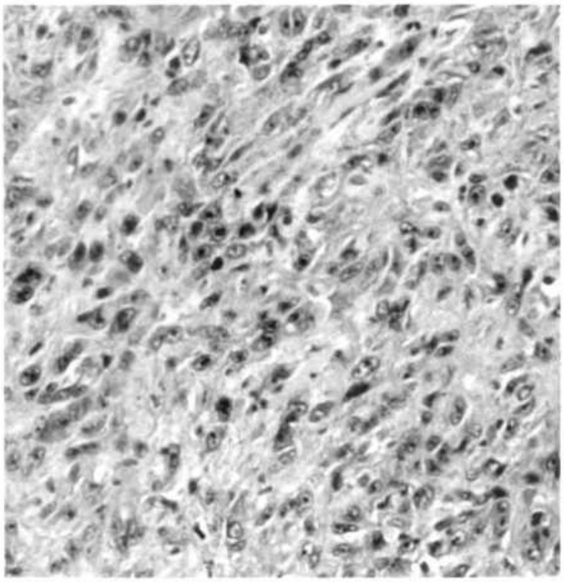

Fig. 1 The histological type of this heterotransplantable tumour shows an anaplastic pattern, spindle cell type (JRC 11). (H and E × 100).

measured with a thermosensor using the thermodependent transmission of light through a gallium-arsenic crystal.

When the weight of the implanted tumour reached 500 to 1000 mg, treatment began under Nembutal anaesthesia. Since a temperature of 44.0°C at the core of the puncturing catheter resulted in 42.5°C at the tumour periphery, a 30-min heating time was selected and single heating was performed in all cases (Fig. 2). For controls, only the puncturing catheter was applied.

The IFNs used in this study were IFN-alpha (human lymphoblastoid interferon, HLBI) and IFN-gamma (recombinant IFN-gamma, S-6810). In the experiment with IFN alone, this was administered daily for 17 successive days. In combined use with hyperthermia, administration was started 60 min before hyperthermia and continued until the first death of a nude mouse occurred. IFN-alpha and IFN-gamma were administered i.m. and i.p. respectively on consecutive days. A single dose was 1×10^5 or 3×10^5 iu (0.1 ml) for IFN-alpha and 3×10^5 or 6×10^5 JRU (0.1 ml) for IFN-gamma. Experimental controls were given 0.1 ml of physiological saline solution.

After implantation of the tumour, its long and short diameters (L) and (S) were measured and from the volume (V mg) $= L \times S^2/2$ according to the spheroidal theory, the rate of inhibition of tumour proliferation was calculated from the mean values for each group. The TRW/CRW ratio (relative mean tumour weight ratio) was determined. The equation for the calculation of TRW/CRW ratio is $Tn/T0 \times C0/Cn$, where relative mean tumour weight ratio; tumour weight for the therapeutic group Tn: day n, tumour weight for the therapeutic group T0: day 0, tumour weight for the control group Cn: day n, tumour weight for the control group C0: day 0. When the calculated value for any group was 42% or lower, this was defined as a positive response; when it was 43% or higher, the treatment was deemed to be ineffective.

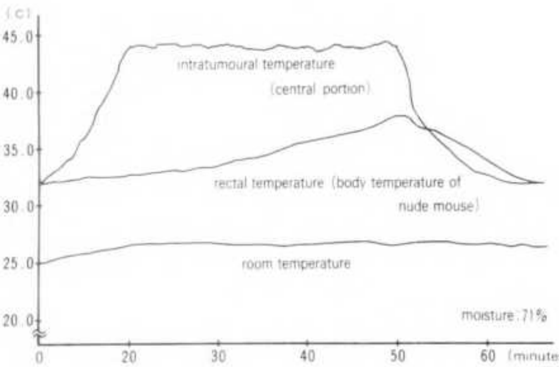

Fig. 2 Changes in the body temperature of the nude mouse during the hyperthermic experiment.

In parallel with this, a histological evaluation was undertaken according to the classification of Shimosato *et al.* (1971) by using the criterion that degeneration equal to or higher than grade III, wherein no viable tumour cells are observed, was an indication of histological effectiveness. Furthermore, since the tumour cell line JRC11 which was used in this study induced a cachectic state in all of the animals, leading to their death 5 weeks after tumour inoculation, the macrobiotic effects of the treatment on nude mice were also examined.

To assess whether any adverse side effects were associated with the treatment, the temporal changes in body weight were compared with those of the controls. Student's *t* test was used for the evaluation of significance.

Results

Effect of hyperthermic therapy alone

After commencement of hyperthermic therapy, the tumours exhibited the same rate of growth as in the control animals and, starting after 2 weeks of therapy, all animals had died by week 3. The ratio of TRW/CRW was 104.5%, indicating ineffectiveness (Fig. 3). There was no grade I histological degenerative change, which also indicated that the treatment was ineffective.

Effect of IFN-alpha and IFN-gamma administration alone

In the experiments in which IFN-alpha in doses of 1×10^5 iu and 3×10^5 iu were administered, no additional tumour suppression was observed when compared with the controls. The tumours showed a TRW/CRW ratio of 95.7% for the 1×10^5 iu group and 93.8% for the 3×10^5 iu group (Fig. 4). No histological anti-cancer effect was observed, indicating that the therapy was ineffective. Similarly, the IFN-gamma group showed no improvement in either the 3×10^5 JRU or the 6×10^5 JRU groups compared with the control group; the TRW/CRW ratios were 102.2 and 90.3% respectively, indicating ineffectiveness (Fig. 5).

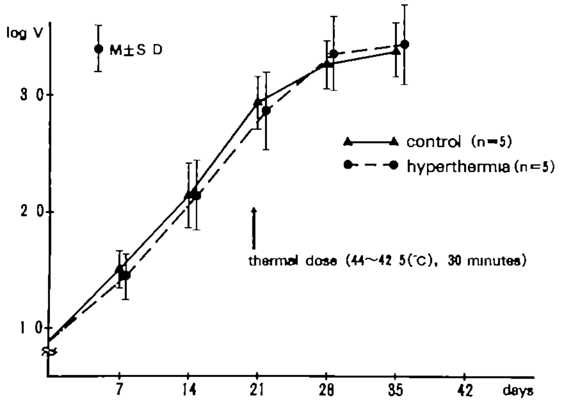

Fig. 3 Growth curve after the commencement of hyperthermic therapy alone against JRC 11 tumours

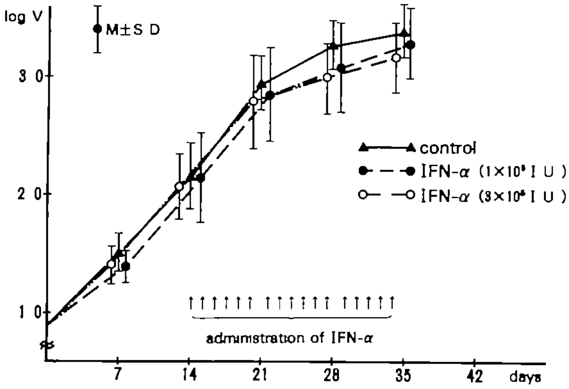

Fig. 4 Growth curve after administration of IFN-alpha Single dose was 1×10^5 or 3×10^5 iu

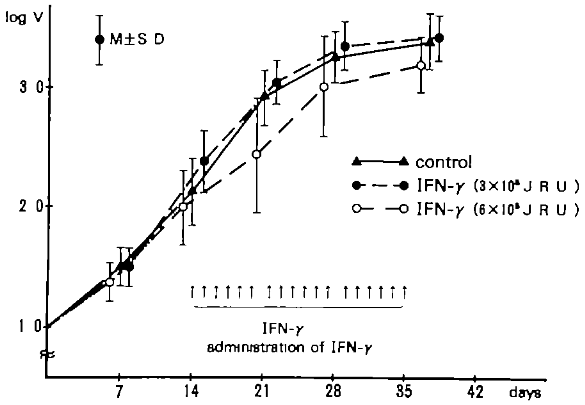

Fig. 5 Growth curve after administration of IFN-gamma. Single dose was 3×10^5 or 6×10^5 JRU

Effect of hyperthermia with concurrent use of IFN

With the concurrent use of IFN-alpha (3×10^5 iu), an experiment was conducted with tumours implanted in 10 animals. From day 42 all of the tumours began to acquire a black-brown colour and, in 10 animals which survived more than 42 days, a reduction in tumour size was observed. On day 56 of treatment (56 days after tumour inoculation), almost complete regression of the tumours had occurred (Figs 6 and 7). Histological examination of the tumours in which the effect of the treatment was apparent revealed that no viable tumour cells were recognisable, which indicated a grade III degeneration (Fig. 8). The 5 nude mice in question have exhibited no sign of recurrence 68 to 195 days after regression of the tumours. Of 10 nude mice (10 implanted tumours) used in the experiment, 5 showed complete disappearance of the implanted tumours and the others (with re-growth and survival time of 61–126 days) showed prolongation of survival. In the experiment in which IFN-gamma (3×10^5 JRU) was administered simultaneously, no efficacy, in comparison with the control group, was found in respect of tumour growth curves, histological degeneration and macrobiotic effect (Fig. 7).

Thus neither hyperthermia alone nor IFN alone produced any improvement in the human renal carcinoma heterotransplanted in nude mice, whereas the combination of hyperthermia with IFN-alpha was seen to be effective.

Discussion

The first report on the effect of hyperthermia was by Busch (1866), who found that sarcoma in a

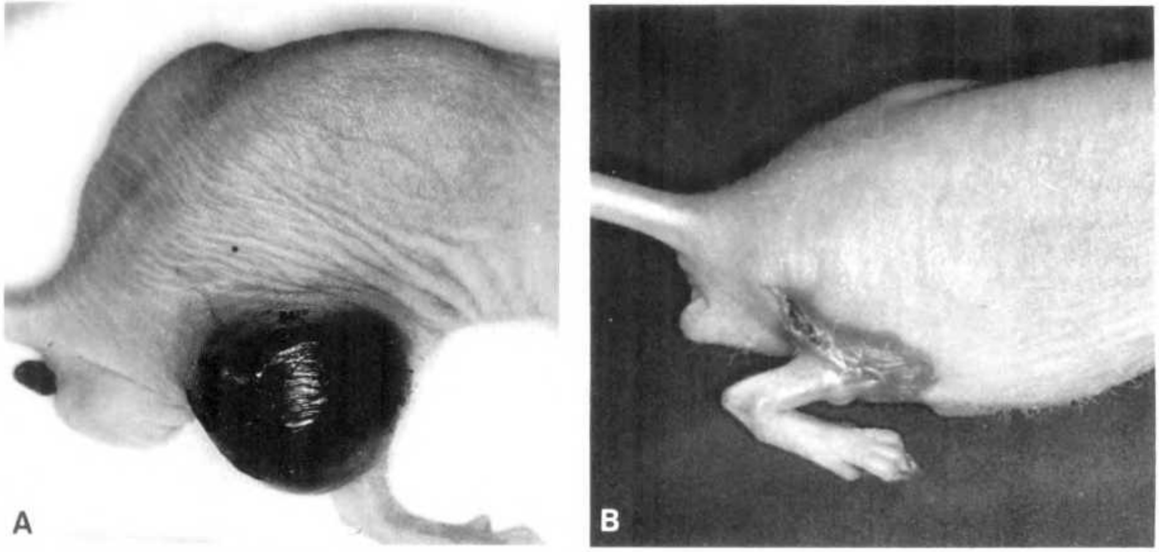

Fig. 6 (A) After 42 days, the tumour starts to turn black-brown. (B) Hyperthermia with the concurrent use of IFN-alpha has a satisfactory effect: 56 days after tumour inoculation, almost complete regression of the tumour was seen.

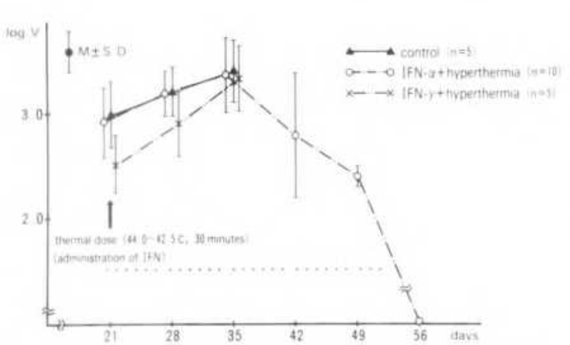

Fig. 7 Growth curve after administration of IFN-alpha or IFN-gamma with hyperthermic treatment. The combination of hyperthermia and IFN-alpha had a satisfactory effect.

patient with erysipelas regressed because of the pyrexia accompanying the disease. Following that, the technical difficulties encountered in the clinical application of hyperthermic therapy caused interest to wane. However, this approach is again arousing interest for three reasons:

(1) The efficacy of auxiliary therapeutic approaches used in conjunction with surgical treatment.
(2) Hyperthermia provides a unique action not possessed by other therapeutic methods.
(3) The basic principles underlying the theory of hyperthermic cancer therapy have finally been elucidated.

The most important and specific aspect of the basic theory of the action of hyperthermia is the series of mechanisms whereby reduction in oxygen consumption caused by a raised tumour cell temperature reduces aerobic saccharolysis. This promotes anaerobic saccharolysis which, in turn, causes a reduction in pH owing to the accumulation of lactic acids in tumour tissues and leads to an increase in the thermosensitivity of the heated lesion (Dietzel, 1983).

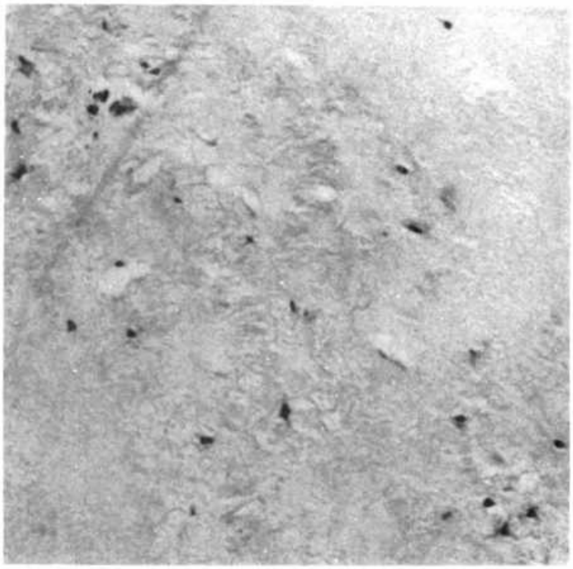

Fig. 8 On day 56, combined treatment with IFN-alpha and hyperthermia showed histological degeneration classified as a grade III change. (H and E × 100).

Following clinical trials of hyperthermia, effects not observed in other forms of treatment have been reported. However, investigations have only just begun into the therapeutic effect of the induction of hyperthermia in renal carcinoma.

The present study has shown that the sole use of hyperthermia on human renal carcinoma serially transplanted in nude mice is ineffective with regard to tumour growth curves and microscopic histological degeneration. This inadequacy may be attributed to the lack of uniform elevation of temperature throughout the implanted tumour and also to the lack of thermosensitivity of the particular tumour employed.

The results of experiments on heat application *in vitro* showed that the hyperthermic effects on tumour cells differed dramatically from those on normal cells at temperatures between 41 and 43°C. This 2°C difference is therefore critically important. In the present study we attempted to heat the tumour from its core, in contrast to the ordinary method in which a water bath heats the tumour from its periphery (Jo *et al.*, 1986). Our method is therefore more satisfactory and provides an excellent approach because the tumour is heated from its hypoxial core, the implanted tumour is in the shape of a balanced ellipsoid, and the characteristics of ultra high frequency waves provide more uniform heating. As previously stated, there were no problems with the heating technique adopted in this experiment. Nevertheless, hyperthermia had no effect on the tumours, perhaps due to their lack of thermosensitivity.

In addition, IFN-alpha and IFN-gamma had no effect on implanted tumours. It is generally accepted that IFN (anti-cancer effects) may be divided roughly into two types: direct influence on tumours and indirect influence via the immune system of the host (Quesada *et al.*, 1983). In the present study, although the direct effect only is conceivable, IFN alone did not markedly reduce the tumours, and this also occurred when hyperthermia was applied alone. According to clinical studies of renal carcinoma, IFN can exert a 20% anti-tumour effect, but this does not exceed the efficacy of other anti-cancer agents (deKernion *et al.*, 1983). In this context, therefore, a search is being made for a better auxiliary therapeutic approach.

We have found only 3 reports on hyperthermia used simultaneously with IFN. The first described the treatment of malignant melanoma using direct intra-tumoural administration of IFN-beta; significant inhibition of tumour growth was reported, which suggested the importance of concurrent administration of IFN with hyperthermia (Nakagawa and Yamada, 1985). Further reports on this type of combination therapy concerned *in vitro* studies. In one of these studies, purified rat IFN preparations proved effective in inhibiting cell multiplication in a rat osteosarcoma cell-line. A pronounced increase in inhibitory activity was found with raised temperature. At 39°C, 20 IFN units/ml appeared to be cytotoxic, whereas incubation of cells with 2000 IFN units/ml at 35°C resulted only in a cytostatic effect (Delbruck *et al.*, 1980). Another report showed that a supra-additive relationship exists between the anti-proliferative effects of IFN-alpha, beta and temperature elevation against human bladder carcinoma cell-lines. In this study, in order to establish the mechanism of the enhanced anti-proliferative effect, the activity of an IFN-induced enzyme, 2′–5′–oligoadenylate synthetase, was measured. IFN-alpha treatment resulted in a significantly greater 2′–5′–oligoadenylate synthetase induction at 39.5°C than at 37°C. However, the mechanisms whereby temperature increases the inhibitory effect of IFN on cell proliferation are unknown (Groveman *et al.*, 1984).

In an analysis of the cell cycle obtained by flow cytometry, IFN-alpha revealed accumulation at the S-phase, while the hyperthermic treatment showed the best sensitivity in the S-phase of the tumour cell cycle. It is considered, therefore, that pre-treatment with IFN-alpha brought about the synchonisation to the S-phase of the cell cycle. This mechanism provided a supra-additive response with the combined use of IFN-alpha and hyperthermic treatment against renal carcinoma (Hayakawa *et al.*, 1985).

As has been stated in this report, hyperthermia in combination with IFN had a positive effect. However, many problems remain unsolved regarding this combination therapy. One is that encountered in determining the thermal dose. Although 43°C for 30 min was used in the present study (Nakagawa and Yamada, 1985), this was based solely on the fact that the nude mouse can tolerate local heating at that temperature for that period. It is apparent, therefore, that the effect of further prolongation of heating time provides material for further exploration.

Another problem relates to the question of which should take precedence, hyperthermia or administration of IFN. The authors have two opinions on this matter:

(1) IFN-alpha can be administered immediately before the commencement of hyperthermia

because the natural-IFN-alpha tolerates a temperature elevation up to 56°C. On the other hand, recombinant-IFN-gamma should not be administered immediately before the commencement of hyperthermia because of its instability at high temperatures.

(2) In our experimental system, single heating was adopted, and it was necessary to administer IFN before hyperthermia so that the synergistic or additive effects during heating could be examined.

Although the effect of IFN is generally considered to be increased when it is connected to receptors (Yamada and Shimoyama, 1983), the mechanism which prompts the induction of the anti-cancer effect of IFN, when used concurrently with hyperthermia, may be that the intra-tumoural IFN level is raised by an increase in the permeability of the tumour cell membrane at elevated temperatures. This is in accordance with the promoting mechanisms considered likely with other anti-cancer agents.

As has been stated, remarkable effects are exhibited by hyperthermia in combination with IFN. Although the approach still requires further examination of the thermal dose and the timing of IFN administration, it provides basic clues to the future introduction of multidisciplinary and collective treatment of renal carcinoma.

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Renal Function after Autotransplantation with Direct Pyelocystostomy. Long-term Follow-up

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Summary—The function of 20 human autologous kidney grafts was studied for 4 to 8 years (mean 5½) after autotransplantation with a direct pyelocystostomy. The indications for the operation were low-grade, low-stage tumour of the renal pelvis and/or ureter, frequently recurrent renal stones and remaining outflow obstruction after pyeloplasty for hydronephrosis.

The wide pyelocystostomy implies reflux of urine from the urinary bladder to the renal pelvis but no significant changes were found in glomerular or tubular function, studied with ^{51}Cr-EDTA clearance, ^{131}I-Hippuran renography, analysis of β_2-microglobulin and total protein excretion in urine, and determination of concentration ability after administration of desmopressin. No increase in the severity or frequency of urinary tract infections was observed.

Since 1977 we have performed renal autotransplantation with direct pyelocystostomy in patients with low-grade, low-stage tumour of the renal pelvis and/or ureter (Pettersson *et al.*, 1984), frequently recurrent renal stones (Pettersson *et al.*, 1983b) and persisting outflow obstruction after pyeloplasty (Pettersson *et al.*, 1983a).

The procedure comprises perifascial nephrectomy, extracorporeal resection of the ureter and most of the renal pelvis and autotransplantation of the kidney to the ipsilateral iliac fossa. A direct anastomosis between the pelvic remnant and the urinary bladder with a diameter of 1 to 2 cm is constructed. In tumour patients, the procedure allows removal of the entire extrarenal part of the urothelium, including the tumour(s) of that renal unit, and future transurethral control of the intrarenal part. In stone patients, the wide pyelocystostomy permits free passage of stones and in patients with previous outflow obstruction a permanent free outflow of urine is obtained.

In a previous study it was shown that extracorporeal preservation of the kidney and autotransplanation *per se* did not affect glomerular or tubular function (Ranch *et al.*, 1985a), and extensive mobilisation of the bladder and fixation to the kidney did not interfere with bladder emptying (Ranch *et al.*, 1985b). The direct anastomosis between the renal pelvis and the bladder implied, however, reflux of urine from the bladder to the renal pelvis as illustrated by the transient dilatation of the calices regularly observed during micturition on cystography (Ranch *et al.*, 1985b).

The aim of this study was to investigate whether the direct pyelocystostomy and the reflux of urine in the long term adversely affected renal function.

Patients and Methods

Between 1977 and 1983, 21 kidneys in 21 patients were autotransplanted with a direct anastomosis between the renal pelvis and the urinary bladder. Long-term follow-up was impossible in 1 patient because of early graft loss (Pettersson *et al.*, 1983b). The mean age of the remaining 20 patients was 52 years (range 32–77), there were 17 men and 3 women. The mean observation time was 5½ years (range 4–8).

Low-grade urothelial tumour(s) of the renal pelvis and/or ureter was the indication for the operation in 9 patients, 1 of whom had a solitary kidney after previous contralateral nephrectomy for a ureteric tumour. Two patients underwent nephroureterectomy on the contralateral side shortly after auto-

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transplantation because of a synchronous tumour of the renal pelvis. In 1 patient a single microscopic lymph node metastasis was found (Pettersson *et al.*, 1984).

Frequently recurrent stones of the upper urinary tract despite prophylactic treatment were the indication for the procedure in 7 patients. In this group, 2 had a solitary kidney, both with a staghorn stone; 1 had aplasia of the contralateral kidney and the other had previously undergone nephrectomy because of stones and repeated infections; 3 patients had medullary sponge lesions, cystine stones or a cholesteatoma of the renal pelvis (Henriksson *et al.*, 1983; Pettersson *et al.*, 1983b).

Persisting outflow obstruction and pain after unsuccessful pyeloplasty was the indication for operation in 4 patients, 2 of whom had such severe pain that they were unable to work. Radiologically, 3 showed pronounced dilatation of the intrarenal collecting system at IVU during forced diuresis and 1 had hydrocalicosis pre-operatively (Pettersson *et al.*, 1983a).

One patient with prostatic hyperplasia and a reduced urinary flow rate was subjected to TUR of the prostate 2 months before autotransplanatation. In 4 patients a TUR was carried out 3 to 19 months post-operatively. Pre-operatively, 7 patients had, or had previously had, positive urine cultures.

All patients were treated with antibiotics post-operatively but no long-term prophylactic treatment was given. If urinary tract infections were found post-operatively, they were treated with antibiotics according to bacterial culture and sensitivity testing.

The pre- and post-operative investigations were directed both at the underlying disease and at renal and urodynamic function. The results of the urodynamic studies have been reported by Ranch *et al.* (1985b).

Urine cultures

Cultures were performed at every check-up on voided urine with a bladder incubation time of at least 4 h. A bacterial count of $\geq 100{,}000$/ml was regarded as significant bacteriuria.

Evaluation of renal function

Serum creatinine concentration was determined at each follow-up. The glomerular filtration rate (GFR) was measured by ^{51}Cr-EDTA plasma clearance (Brøchner-Mortensen, 1972). This method gives the total GFR. To obtain the GFR of the transplant, in patients with 2 kidneys, the relative function of each kidney was determined by ^{131}I-Hippuran renography using an individualised background subtraction technique (Haugstvedt *et al.*, 1980). Proximal tubular function was assessed by determination of the β_2-microglobulin excretion in urine (Wibell, 1974). Distal tubular function was evaluated by testing concentration ability after intranasal inhalation of desmopressin (Minirin, Ferring, Sweden) (Delin *et al.*, 1978).

The functional parameters were checked every 6 or 12 months.

Statistical methods

Conventional statistical methods were used to calculate the mean and standard deviation of the mean.

Wilcoxon's matched pairs signed rank test was used to test the null hypothesis that there could be a change in renal function during follow-up. The null hypothesis that good renal function could be correlated with a short observation time was tested using Spearman's rank correlation test. The patients were also divided into 2 subgroups, 1 without infection after autotransplantation and the other with 1 or more infection episodes. Wilcoxon's signed rank test was applied to assess changes in renal function during the follow-up period within these subgroups. Wilcoxan's rank-sum test was also used to see if there was any difference between the subgroups.

Results

The total GFR, GFR of the transplant and maximum concentration ability during the observation period for all patients are presented in Figures 1 and 2. The values at 6-monthly intervals are expressed as percentage changes from the first post-operative value. No significant changes were found when the mean value and the standard deviation of the mean of the percentage changes at each 6-monthly period were compared with the first post-operative value, nor was there any significant difference between the first and last post-operative value with regard to total GFR, GFR of the transplant or concentration ability during the entire observation period. There was no significant correlation with the length of follow-up.

The total GFR, GFR of the transplant and concentration ability in patients with and without post-operative urinary tract infection are presented in Figures 3 and 4. There were no statistically significant changes in the mean of the percentage changes. No significant changes were found in the

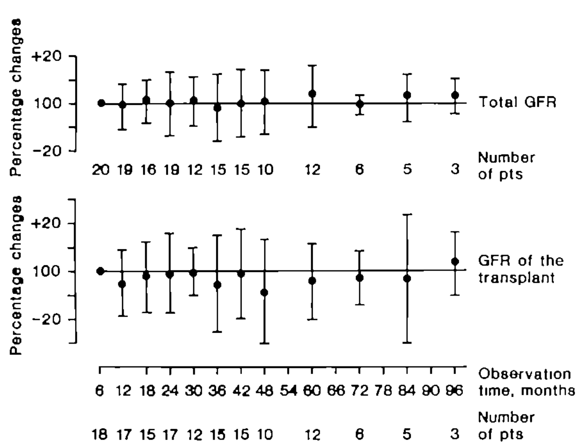

Fig. 1 Total GFR and GFR of the transplant. Percentage changes (mean ± SD) from first post-operative value of the total GFR and GFR of the transplant. The number of patients at each observation is shown

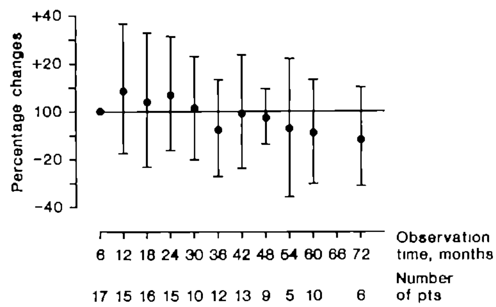

Fig. 2 Maximum concentration ability Percentage changes (mean ± SD) from first post-operative value The number of patients at each observation is shown.

total GFR, GFR of the transplant or concentration ability, either within or between the groups.

Serum creatinine values were within the normal range (< 115 μmol/l) in all patients but 5. The latter patients had a moderately raised level (116–155 μmol/l), 3 of them even pre-operatively.

The excretion of β_2-microglobulin in urine remained unchanged during the observation period in most patients. Values above the normal range were seen in 2 patients; 1 had a phenacetin nephropathy and the other had urinary tract infections both before and after the operation. In another 2 patients, increased values were occasionally registered in connection with infection and recurrent tumour growth. No patient showed raised levels of total urinary protein and none developed hypertension post-operatively.

In 9 patients all pre- and post-operative urine cultures were negative; 5 patients had one positive culture during the follow-up period; 2 of them did not have infection pre-operatively. The other 6 patients had 2 or more infections after autotransplantation, 5 of them also having had positive cultures pre-operatively. Two of the 6 patients had one episode of acute pyelonephritis and the other 4 had asymptomatic infections, 1 of them having a medullary sponge kidney with multiple stones and permanent *Klebsiella* infection.

The autotransplanted kidney was examined post mortem in 4 patients and after nephrectomy in 1.

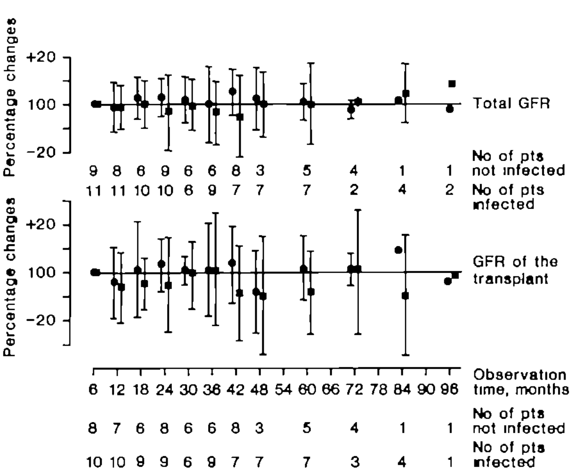

Fig. 3 Total GFR and GFR of the transplant in patients with and without urinary tract infection Percentage changes (mean ± SD) from first post-operative value of the total GFR and GFR of the transplant ■ infected patients. ● non-infected patients. The number of patients at each observation is shown.

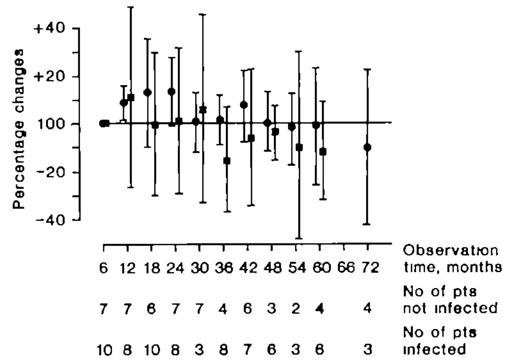

Fig. 4 Maximum concentration ability in patients with and without urinary tract infection Percentage changes (mean ± SD) from first post-operative value. ■ infected patients. ● non-infected patients The number of patients at each observation is shown.

In 1 patient, with no pre- or post-operative infections, no appreciable inflammatory lesions were found. In the other 4, pyelonephritic changes were observed. The significance of these changes is difficult to evaluate because of concomitant phenacetin nephropathy, recurrent infection stones, recurrent TURs of infiltrating bladder carcinoma in combination with severe urinary tract infections, and extensive local recurrence in the kidney, respectively.

Outcome of the Original Disease

Tumour patients

In 4 patients no recurrent tumour was observed. In 3 patients recurrences were coagulated transurethrally; in 1 of them an infiltrating recurrence necessitated removal of the transplant and regular haemodialysis 53 months after autotransplantation. One patient died in an accident 14 months after transplantation. No tumours of the bladder or pelvis or metastases were found at autopsy. One patient died after 27 months as a result of metastases of a squamous cell differentiated bladder carcinoma. The renal pelvis and parenchyma were free of tumour at autopsy. The patient with a single microscopic lymph node metastasis died after 48 months with generalised tumour growth. The follow-up time was 3½ to 6 years (mean 5).

Stone patients

One patient passed recurrent stones spontaneously on two occasions. The others have been free of recurrence except for the one with a medullary sponge kidney. One patient died of myocardial infarction 48 months post-operatively.

Hydronephrosis patients

Three patients became free of pain and have remained so. One has a pricking sensation in the graft region but this does not reduce his working capacity. The patient with pre-operative hydrocalicosis at diuresis IVU had slightly dilated calices post-operatively. The other 3 had slender calices, only slightly dilated during voiding.

Discussion

Follow-up of the 20 autologous kidney grafts with direct pyelocystostomy revealed no significant changes in glomerular or tubular function during an observation period of up to 98 months. This was true whether or not urinary tract infection was present. The different diseases which were the indications for the operation were in most cases successfully treated by the procedure.

Direct pyelocystostomy was first described by Hess (1929) in a patient with crossed renal dystopia. Since then, it has mainly been used in renal transplantation surgery as a rescue procedure to replace allograft ureters with impaired circulation (Lindstedt *et al.*, 1981).

Anastomosis between the renal pelvis and the urinary bladder may also be achieved by raising a Boari flap from the bladder to the renal pelvis of an autotransplanted kidney (Olsson and Idelson, 1980) or by the interposition of an ileal segment between the renal pelvis and the bladder (Goodwin *et al.*, 1959). These procedures have been used not only to restore communication between the kidney and the bladder in patients with damage to the ureter but also to permit the spontaneous passage of recurrent stones. The interposition of an ileal segment has several drawbacks, however, as it is often complicated by infections, electrolyte imbalance and renal damage (Tanagho, 1975).

Autotransplantation of a kidney with a direct pyelocystostomy was first used in a patient with a low-grade, low-stage tumour of the pelvis of a solitary kidney (Pettersson *et al.*, 1979). That patient was rapidly followed by others with urothelial tumours of the upper urinary tract at the same time as the indications for the procedure also came to include failed pyeloplasty and recurrent stones.

Several objections can, however, be raised against using autotransplantation with a direct anastomosis between the renal pelvis and the bladder in these contexts. One is the consequence for renal function of taking out the kidney, cooling it and revascularising it after an ischaemia time of several hours. In a previous study we reported that the glomerular and tubular function of the grafts was not significantly changed by the extracorporeal preservation and the autotransplantation procedure (Ranch *et al.*, 1985a). It is true that one graft was lost but that was the remnant of a kidney that had been subjected to partial nephrectomy 3 times in a patient with bilateral calcified and infected meduallary sponge lesions. Today, that patient would not have been accepted for the procedure.

Another objection which could be raised is the long-term effect on graft function of the direct wide pyelocystostomy. This anastomosis implies reflux of urine from the bladder to the renal pelvis. As previously mentioned, dilatation of the calices is also regularly observed during micturition on cystography (Ranch *et al.*, 1985b). According to paediatric experience, urinary reflux and infection are known to have the potential to cause chronic pyelonephritis (Steinhardt, 1985). There is, however, still controversy as to whether reflux of sterile urine may cause renal damage or not. Some investigators believe that scars rarely occur in kidneys beyond infancy and that, when present, they seldom progress even when reflux and infection coexist (Lancet, 1978; Ransley and Risdon, 1978; Huland *et al.*, 1986). If, however, reflux is present together with obstruction, progressive renal damage is the rule (Koff *et al.*, 1979). Pressure in the pelvis and calices is the same as in the bladder, which is normally low during the entire filling phase of the bladder. The kidney is thus probably exposed to increased pressure only during the micturition phase itself. This is in agreement with observations during cinecystography, where transient dilatation of the calices was observed only during micturition (Ranch *et al.*, 1985b). These short periods of raised pressure have not caused any significant changes in glomerular or tubular function during a maximum follow-up of 98 months. It should be stressed, however, that it is essential to make sure that the patient does not develop an infravesical obstruction with high pressure during voiding and possibly also increased pressure at rest because of bladder hypertonicity. To avoid this risk, 1 patient in the present series underwent TUR of the prostate before autotransplantation and another 4 patients after the procedure.

The direct reflux allows bacteria in the bladder urine to reach the renal pelvis and calices and a lower urinary tract infection will also immediately affect the upper urinary tract in these patients. They have therefore been checked regularly with regard to bacteria in the urine, but infection has not been a serious problem in these patients, even in the presence of slightly increased residual urine.

In the present series, neither permanent reflux nor infections seem to have affected renal function. In a study including 7 patients with or without a Boari flap (Bodie *et al.*, 1986), no sign of decreased renal function was found during a follow-up period of 6 years, as measured by repeated serum creatinine determinations and radiorenography. Lindstedt *et al.* (1981) found no evidence of chronic pyelonephritis in the allograft of their patient 9 years after direct pyelocystostomy. Otherwise, it may be difficult to decide whether the declining function of a renal allograft with a direct pyelocystostomy is secondary to chronic rejection or to the direct pyelocystostomy.

The ^{51}Cr-EDTA clearance, together with calculation of the side distribution using ^{131}I.Hippuran renography, provided a measure of the GFR of the transplant. This procedure eliminates misinterpretation due to compensatory hypertrophy of the contralateral kidney. A reduction in distal tubular function is evident as a decrease in concentration ability. If one kidney, presumably the autotransplanted one, reduces its concentration ability, it will lead to dilution of the normally concentrated urine from the other kidney. A significant decrease in concentration ability would therefore suggest damaged distal tubules, most probably those of the autotransplanted kidney. Correspondingly, an increased concentration of β_2-microglobulin in the urine would indicate damage to proximal tubules in the autotransplanted kidney. Pyelonephritis in this kidney would also increase the total amount of urinary proteins.

In conclusion, both glomerular and tubular function remained intact in 20 renal autografts with a direct pyelocystostomy during a follow-up period of up to 8 years. We believe that the reflux of urine which is regularly observed in these patients does not adversely affect the transplanted kidney as long as there is no infravesical obstruction and urinary infections are treated when possible.

Acknowledgement

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Anterior Transperitoneal Approach to the Upper Urinary Tract with One-stage Bilateral Procedure

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Summary—A total of 109 unilateral and 4 bilateral upper urinary tract conditions were treated surgically from 1975 to 1985 by the anterior transverse transperitoneal approach; 26 of these were malignant conditions and 87 were benign. The approach gives good access to the kidney, its pedicle and the upper ureter. There is no increased risk of peritonitis or paralytic ileus due to urinary leak.

One-stage bilateral surgical procedures were performed in 4 cases. There was no added risk to the patients. It allows both kidneys to recover simultaneously and provides the opportunity of examining the other intra-abdominal organs.

Operations on the upper urinary tract are the commonest open surgical procedures in urological practice and are likely to remain so in spite of rapid advances in percutaneous and extracorporeal techniques.

Various approaches and incisions to the kidney and upper ureter have been described. The commonest approach is through the loin and this may be through a subcostal, transcostal or supracostal incision, depending on the position of the kidney, the physique of the patient and the preference of the surgeon. A thoraco-abdominal approach for large renal masses and a lumbotomy for re-operation on the upper tract may be indicated. The anterior transperitoneal approach has been advocated for renal tumours as the vascular pedicle can be secured before the kidney is handled in order to reduce the risk of intravascular dissemination of tumour cells. We present our experience with the anterior transverse transperitoneal approach to all high urinary tract lesions for dealing with unilateral and bilateral conditions.

Patients and Methods

A retrospective analysis of 113 patients with upper urinary tract lesions requiring surgery between 1975 and 1987 was undertaken. Of these 109 had unilateral and 4 had bilateral conditions. All 113 patients were treated through an anterior transperitoneal approach as described by Poutasse (1961) with some modifications.

For unilateral conditions the patient is placed in the supine position with a sandbag under the ipsilateral loin to bring the kidney to a more anterior position. The transverse incision starts halfway between the xiphisternum and the umbilicus and extends towards the tip of the eleventh or twelfth rib. All structures of the anterior abdominal wall are divided in the line of the incision. The ipsilateral colon is mobilised medially (together with the duodenum on the right side) to expose the perinephric fascia. The vascular pedicle, renal pelvis, ureter and kidney are now readily accessible.

For bilateral conditions the patient is placed in the supine position with sandbags under each loin. The incision arches upwards with its midpoint halfway between the xiphisternum and the umbilicus. Ascending and descending colons are mobilised medially to expose both kidneys lying in their perinephric fascia.

Closure of these incisions is in layers and the renal area is usually drained.

There were 58 males (58.3%) and 55 females (48.7%) with an age range of 2 to 76 years; 36 patients (31.8%) were above the age of 60 years, 55

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(48.7%) were between 30 and 60 and 22 (19.5%) were less than 30 years old.

Of the 109 unilateral procedures, 63 patients underwent nephrectomy or nephro-ureterectomy for renal carcinoma (21), calculus disease (17), chronic pyelonephritis (10), hydronephrosis (5), transitional cell carcinoma (5), renal cysts (2), hypertension (1), hypoplasia (1) and pyonephrosis (1); 25 patients had Anderson Hynes pyeloplasties for congenital pelviureteric junction obstruction, 20 patients had pyelolithotomies or pyelonephrolithotomies and 1 had a partial nephrectomy for upper pole calculus with hydronephrosis. When indicated, cystoscopy, retrograde ureterography or optical urethrotomy were performed immediately prior to the renal surgery. In addition, 6 of the 109 patients had elective appendicectomies, 1 had an appendicectomy and repair of a para-umbilical hernia, 2 underwent cholecystectomy and 1 had a choledocho-duodenostomy.

Four patients with bilateral upper urinary tract lesions had surgery to both sides through the same anterior incision (Fig. 1). A 56-year-old male with stones in the right pelvis and left ureter had a right pyelolithotomy and a left ureterolithotomy. A 31-year-old male with a stone in the right pelvis and 2 stones in the left ureter had similar surgery. A 46-year-old female with a right gross hydronephrosis due to pelviureteric junction obstruction and a non-functioning left kidney underwent a right Anderson Hynes pyeloplasty and a left nephrectomy. A 72-year-old female had bilateral staghorn calculi (Fig. 2) and both were removed by bilateral pyelonephrolithotomy (Fig. 3).

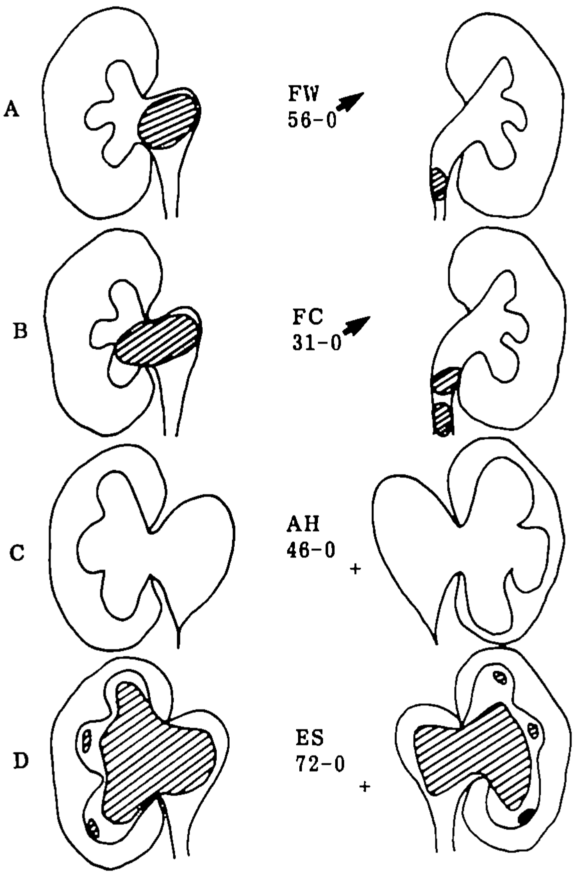

Fig. 1 Diagrammatic representation of bilateral upper urinary tract lesions

Results

Unilateral operations

Urinary leaks developed in 10 patients following reconstructive procedures; 8 of these required the insertion of a stent and the other 2 responded to conservative treatment. None of these patients developed peritonitis or paralytic ileus and leaked urine drained away via a drainage tube. Wound infections occurred in 7 patients (6.4%) but there was no incidence of burst abdomen or incisional hernia. Nine patients (8.2%) became pyrexial. In 6 cases there was a urinary tract infection and 3 patients developed chest infections. All were treated effectively with the appropriate antibiotics. Secondary haemorrhage, paralytic ileus (not due to urinary leakage) and a faecal fistula (in a patient who had a previous pyonephrosis drained) occurred in 3 separate patients. All responded satisfactorily to conservative treatment. One 53-year-old female who was uraemic due to calculus disease on admission and underwent emergency nephrolithotomy and ureterolithotomy died on the twentieth post-operative day following cardiac arrest and aspiration of gastric contents.

The average inpatient stay for the 63 nephrectomy patients was 12.68 days (range 3–48); 54% of the patients had been discharged by the tenth post-operative day; 1 patient discharged herself against medical advice on the third post-operative day with drain and sutures but returned to the out-patient clinic having suffered no ill effects.

One male patient stayed for 33 days for social reasons.

For patients following removal of stone the average stay was 11.35 days (range 7–22) and the average stay for patients who had undergone pyeloplasty was 15.2 days (range 7–34) due to urinary leakage.

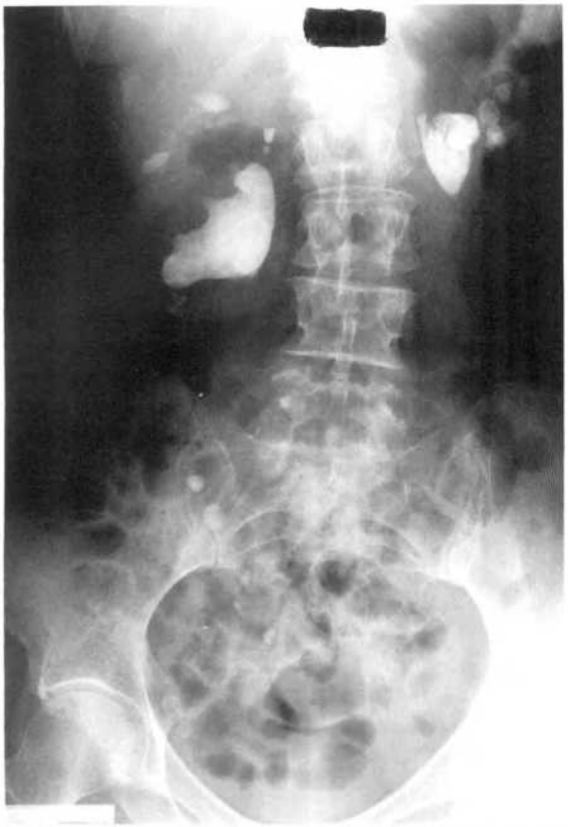

Fig. 2 Radiograph of case D in Figure 1 with bilateral staghorn calculi.

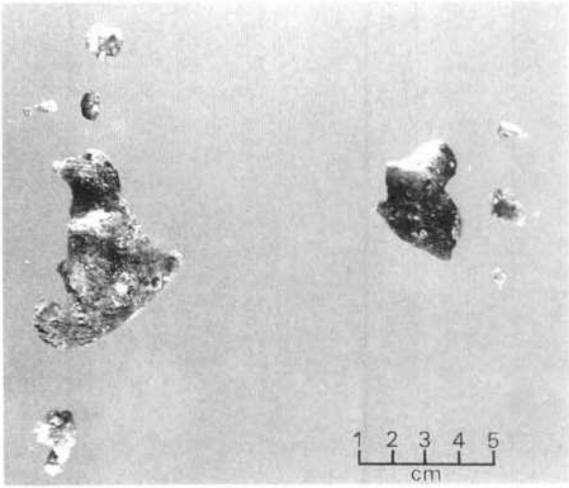

Fig. 3 Bilateral staghorn calculi removed at one-stage surgical procedures.

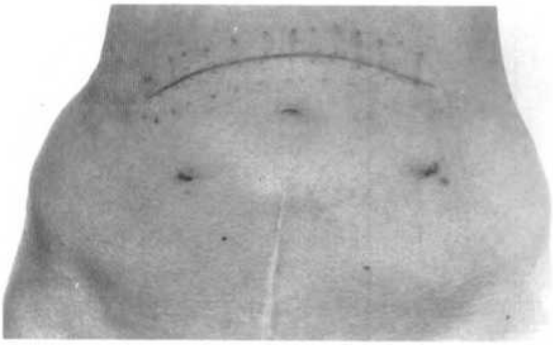

Fig. 4 Well healed main wound and drain sites 2 weeks post-operatively (Figs 2 and 3).

Bilateral operations

One patient had a urinary leak 14 days after pyeloplasty which required the insertion of a stent and she stayed for 35 days (Fig. 1C). One patient had a post-operative pyrexia following right pyelolithotomy and left ureterolithotomy treated conservatively. He was discharged on the seventh post-operative day (Fig. 1B). One patient had a drain site leakage following bilateral pyelolithotomies; this was treated conservatively and the patient was discharged on the fourteenth post-operative day (Figs 1D and 4).

Discussion

Poutasse (1961) described the technique of the anterior approach to upper urinary tract surgery which he used in over 250 operations and discussed its advantages and disadvantages. Linke *et al.* (1976, 1978) described a further 13 patients (15 kidneys) and 18 patients (20 kidneys) treated with the anterior approach, in 3 of whom bilateral stones were removed with a one-stage procedure. Proca (1981) claimed a distinct advantage of the technique when removing stones from horseshoe kidneys in 13 patients (7 unilateral and 6 bilateral stones). Dermler *et al.* (1983) described 14 patients with bilateral nephrolithiasis who underwent simultaneous bilateral lithotomy safely and discussed the advantages of this approach. Rao and Lakshman (1985) reported 24 selected cases of bilateral urinary tract lesions where single-stage corrective surgical procedures were performed. Many advantages were claimed.

The anterior transperitoneal approach allows good access to both kidneys and vascular pedicles. Positioning of the patient is easy and intra-operative radiography can be carried out more readily. It allows the surgeon the chance to examine other intra-abdominal structures and to carry out other surgical procedures simultaneously. There is no excess risk of peritonitis or paralytic ileus due to urinary leak.

Blandy and Man meet Singh (1976) advocated an aggressive approach to staghorn calculi with early surgery and complete removal of calculi with early even when asymptomatic. A one-stage procedure eliminates concern about the conditions of the contralateral kidney and avoids the controversy as to which kidney should be operated upon first. A single operation with one anaesthetic and one admission benefits the patient and allows an earlier return to work. There is a reduction in hospital stay and operating time. It is felt that one-stage bilateral surgical procedures on the kidneys have no added risk using modern techniques.

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Ureterolithotripsy: Report of 1000 Cases

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Summary—A series of 1000 patients with calculi of the ureter at various levels were treated by ureteroscopy and lithotripsy over a period of 27 months. The overall success rate was 88.8%. Stones in the upper third of the ureter were removed in 15 of 39 patients. Calculi in the middle third were successfully removed in 52 of 102 patients. A success rate of 95.5% was achieved for calculi of the lower ureter. Per-operative complications included 10 ureteric perforations, 4 of which were treated surgically and 6 conservatively. Urography, performed in 520 patients 3 months post-operatively, showed 12 ureteric strictures; 9 of these were treated by insertion of a self-retaining pig-tail catheter and 3 required an operation. Ureterolithotripsy appears to be the method of choice in the management of ureteric calculi.

Ureteroscopy was performed for the first time in a young boy with pasterior urethral valves by Young in 1912 using a rigid cystoscope and was reported a few years later (Young *et al.*, 1929). The routine use of ureteroscopy began in 1976 and improvements in design have now established it in the diagnosis and management of ureteric diseases and mainly lithiasis. This report summarises our experience in 1000 cases of ureterolithotripsy.

Patients and Methods

Between February 1985 and May 1987 we treated 1000 patients (621 male and 379 female) with ureteric stones. The youngest patient was 18 years old and the oldest 76. The calculi were in the upper third of the ureter in 39 patients (4%), in the middle third in 102 (Lyon *et al.*, 1979; Clayman *et al.*, 1984) and in the lower third in 859 patients (86%); 19 patients had more than 1 stone. The indications were those already established for the management of ureteric calculi, *i.e.* dilatation of the upper tracts, recurrent infection and recurrent renal colic. The study did not include patients who had had ureteroscopy for the removal of ureteric "steinstrasse" following ESWL.

All patients were investigated pre-operatively (full blood count, blood urea nitrogen, electrolytes and IVU). A plain abdominal X-ray was obtained a few hours prior to treatment. The method of performing ureteroscopy has been described by Lyon *et al.* (1978) and Perez-Castro and Martinez-Pineiro (1980). Anaesthesia was either general, epidural or spinal. Simultaneous fluoroscopy was seldom used. The stones were eliminated by ultrasound fragmentation, forceps extraction or a combination of the two. The operative time was 10 to 50 min. A ureteric catheter was inserted at the end of the procedure and remained *in situ* for 24 h (occasionally for 48 h if ureteric trauma had occurred).

Results

Irrespective of the location of the stone, 888 lithotripsies were successful. Of the 39 patients (23 male and 16 female) with lithiasis of the upper third of the ureter, lithotripsy was successful in 15 (38.5%) (5 male and 10 female). It was significantly easier to negotiate the upper third of the ureter in female patients. Of the 24 patients in whom lithotripsy failed, the stone was reached in 8 cases but moved to the kidney soon after lithotripsy started; in 16 cases the stone was not reached with the ureteroscope but was successfully pushed into the kidney with a ureteric catheter and was subsequently disintegrated by ESWL.

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In 102 patients with lithiasis of the middle ureter (68 male and 34 female), lithotripsy was successful in 52 (51%) (13 male and 29 female). In 10 patients the stone was not reached, in 6 there was ureteric perforation and the procedure was abandoned and in 34 the fragments were too large to be removed and the Zeiss loop was used.

In 859 patients with stones in the lower third of the ureter (530 male and 329 female), lithotripsy was successful in 827 (95%). Of the rest, 8 patients failed because the stone moved to the kidney, in 6 the stone was not negotiated and these patients were operated upon, in 4 the ureter was perforated and the procedure was abandoned and in 22 cases large fragments remained and were subsequently removed with a Zeiss loop.

Discussion

Although ureteric lithiasis may now be managed successfully by ESWL, ureterolithotripsy seems to be the method of choice because it does not require expensive technology and is a fast and safe procedure in the hands of an experienced endoscopist. The success rate 2 years ago was between 60 and 70% but with increasing experience it is now over 85% (88% in the present series for stones in the lower ureter). The success rate for calculi in the middle and upper thirds has also increased (Lyon *et al.*, 1984; Jenkins, 1986; Lupu *et al.*, 1986; Weinberg *et al.*, 1987). Clayman *et al.* (1984) reported a success rate of 67% for stones in the middle and upper thirds.

Good dilatation of the ureteric orifice with metal or balloon dilators is a prerequisite for successful ureteroscopy. Simultaneous fluoroscopy, especially for low ureteric stones, is not necessary despite reports to the contrary from other centres (Coleman *et al.*, 1984; Weinberg *et al.*, 1987). Serious complications were rare; of the 10 ureteric perforations only 4 required immediate surgical intervention. Strictures were observed in 2.3% of cases.

It is concluded that ureteroscopy is a quick and inexpensive method for the management of ureteric stones. It has no serious complications but does require appropriate instrumentation and immaculate surgical technique if a high rate of success is to be achieved.

Immediate complications in the present series were 10 perforations; 6 of these patients were managed conservatively with the insertion of a ureteric catheter and 4 were operated upon immediately for reconstruction of the ureter.

All patients were asked to have an IVU 3 months after lithotripsy and 520 did so. Ureteric strictures were observed in 12 patients; in 9 of these a self-retaining catheter was inserted and 3 underwent ureteric reconstruction. No reflux was observed in 520 patients who, 3 months following lithotripsy, were examined using retrograde cystography.

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Physical Growth Velocity during Conservative Treatment and following Subsequent Surgical Treatment for Primary Vesicoureteric Reflux

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Summary—Physical growth was studied in 6 males and 16 females during 1 year of antimicrobial prophylaxis and during the 2 years following subsequent surgical treatment for severe primary vesicoureteric reflux. Surgery was performed between the ages of 2 and 8 because of either repeated breakthrough infection or persistence of grade III or IV reflux. Height and weight velocities were calculated as yearly rates and then converted into interquartile ratios (IQRs).

Neither the mean centile height nor weight attained varied significantly between that at entry, after 1 year of medical treatment and at 2 years after surgery. However, the mean IQR for height velocity (±sem) rose significantly from −0.61 (±0.45) during antimicrobial prophylaxis to 0.54 (±0.25) following surgery. Similarly, the mean IQR for weight velocity rose significantly from −0.63 (±0.50) during medical treatment to 0.47 (±0.24) following surgery.

These results suggest that surgical treatment is preferable to continued medical treatment in patients with severe primary vesicoureteric reflux who fail to respond to a trial of antimicrobial prophylaxis.

Both the medical and surgical treatment of vesicoureteric reflux can prevent ascending urinary infection and the subsequent development or progression of renal scarring (McRae *et al.*, 1974; Edwards *et al.*, 1977; Atwell *et al.*, 1978; Aladjem *et al.*, 1980; Atwell and Cox, 1981; Ginalski *et al.*, 1986). Recent evidence suggests that neither treatment fully protects the kidneys from further damage and that when patients with primary vesicoureteric reflux are allocated on a random basis to either treatment, neither appears preferable (Birmingham Reflux Study Group, 1983, 1987). Most previous studies of the effects of either treatment have examined changes in renal function and renal growth to assess these effects. Although changes in physical growth have been used to standardise changes in renal growth, changes in physical growth *per se* have formed the basis of few reports (Merrell and Mowad, 1979; Smellie *et al.*, 1983), none of which have compared medical and surgical treatment.

This study investigated changes in growth and growth velocity in 22 patients with primary vesicoureteric reflux during 1 year of medical or conservative treatment and during the 2 years following subsequent surgical treatment.

Patients and Methods

A series of 6 males and 16 females between the ages of 2 and 8 years underwent ureteric reimplantation for primary vesicoureteric reflux at a single centre from 1976 to 1983. All patients had normal serum creatinine and were treated conservatively with continuous low-dose prophylactic antimicrobial therapy for at least 1 year before operation, and were maintained on antimicrobial prophylaxis for 1 month after operation. Patients who underwent ureteric reimplantation at an age outside the range described above were excluded. Patients with primary vesicoureteric reflux who were treated with antimicrobial prophylaxis but who were not subsequently treated surgically were also excluded, to

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restrict this study to a comparison of patients undergoing both medical and surgical treatments.

Intravenous urography and micturating cystography were performed at presentation and the latter repeated after 1 year of conservative management. Micturating cystography was performed at least 2 weeks after any presenting or breakthrough infection had been eradicated. Vesicoureteric reflux was graded using the classification of Smellie *et al.* (1981) (Edwards *et al.*, 1977): grade I, reflux confined to the lower ureter; grade II, reflux up to the kidney only on voiding; grade III, reflux up to the kidney during bladder filling; grade IV, reflux up to the kidney accompanied by some degree of ureteric or renal pelvic dilatation, or both. Cytoscopy was performed at presentation and the position and configuration of the ureteric orifices noted using the classification of Lyon *et al.* (1969).

Patients were started on low-dose continuous antimicrobial prophylaxis at the time of the first visit unless treatment for urinary tract infection was clinically indicated, in which case prophylaxis was begun after successful treatment of the infection. The prophylaxis given was 1 to 2 mg/kg trimethoprim, either alone or as co-trimoxazole, or nitrofurantoin, as a single nightly dose. All patients were encouraged to void at regular intervals, avoid constipation and maintain an adequate fluid intake. After one subsequent visit for the assessment of each patient's investigations and clinical progress, all patients were seen on a 3-monthly basis for clinical assessment, urine analysis and culture, unless more frequent clinic visits became necessary because of a return of symptoms or proven infection.

Surgery was performed because of repeated breakthrough infection (6 patients) or persistence of grade III or IV reflux (16 patients). Ureteric reimplantation was carried out by a modified Leadbetter–Politano technique and was followed by 1 month of antimicrobial prophylaxis in each patient. During the subsequent 2 years, all patients were seen on a 3-monthly basis for clinical assessment, urine analysis and culture. Further urinary tract infection was treated by appropriate courses of antibiotics, but prophylaxis was not subsequently continued. If all was well, intravenous urography was performed 3 months after operation to exclude ureteric obstruction, and micturating cystography was carried out 12 months after operation to check that reflux was abolished. The data presented here are restricted to the period ending 2 years after surgery, although follow-up has since been maintained on all patients.

Measurements of each patient's height and weight were made at each visit by trained staff familiar with a standard technique (Buckler, 1979). The occasion of the last measurement of height and weight before ureteric reimplantation was taken as the end of the period of observed growth during conservative treatment, and also as the start of the period of observed growth following surgery. Both the heights and weights attained were converted into centiles by reference to standard charts (Tanner *et al.*, 1966). Growth velocities were estimated as yearly rates from the differences in height and weight over the year of conservative treatment immediately prior to surgery, and over the 2 years following subsequent surgical treatment. Since these intervals were rarely exactly 1 or 2 years, the intervals were considered as decimals of a year and yearly velocity rates then calculated. The velocities were taken as representative of the mid-points of these intervals.

The analysis of growth velocities was confined to the period of growth during which height and weight normally increase in a regular manner, *i.e.* between the ages of 2 and 10 for boys, and 2 and 8 for girls (Tanner *et al.*, 1966; Tanner and Whitehouse, 1976). This period of regular growth is readily appreciated by reference to standard charts, which also demonstrate that between these ages height and weight velocity normally change in an almost linear manner. In order to account for this change, each velocity rate was converted into an interquartile ratio. IQRs were taken as the ratio of the observed difference from the mean at any age to the interquartile difference at that age, using appropriate height and weight velocity tables (Tanner *et al.*, 1966). IQRs were used rather than standard deviation scores since standard deviations were not available for weight. Height and height velocity in the normal growing population are distributed normally, and although the distribution of weight and weight velocity in the normal growing population displays some skewness, the t test was used throughout, since the raw data in this study showed little kurtosis or skewness, and since the growth velocities were converted into IQRs.

Results

The Table shows the clinical features of the 22 patients and lists the cystographic and cystoscopic grading of one ureter for each patient; when both ureters were affected, only the more severely affected ureter was listed. Of these 22 ureters, 2 had orifices of a normal configuration, 6 were of stadium shape, 12 were of horseshoe shape, and 2 were of

Table Clinical Features of 22 Patients

No. of patients		
Male		6
Female		16
Age (years)		
Mean (range)	5 83 (2 33–8 08)	
*Cystographic grading of reflux		
II		1
III		8
IV		13
*Cystoscopic grading of ureteric orifices		
A		3
B		11
C		8
Ureteric reimplantation		
Unilateral		8
Bilateral		14
No. of patients with at least 1 urinary tract infection		
During 1 year of conservative treatment		5
During 2 years following reimplantation		5

*Describes the more severely affected side

golf hole shape. Reflux persisted in all 22 ureters, becoming more severe in 8. Of the 36 ureters reimplanted in 22 patients, 3 became partially obstructed in 3 patients. Repeat reimplantation was successful in all 3 patients. No patient was found to have vesicoureteric reflux after surgical treatment.

Figures 1 and 2 show the centile heights and weights attained by each patient at specified times in relation to treatment. The mean centile height attained was 50.8 (sem = ±5.6) at the start of the conservative treatment, falling to 48.4 (±5.3) immediately before surgery and rising to 51.4 (±5.0) at 2 years after surgery. The mean centile weight attained was 46.7 (±6.3) at the start of conservative treatment, falling to 45.1 (±6.2) immediately before surgery and rising to 49.8 (±6.0) at 2 years after surgery. At no time was the distribution of heights or weights attained significantly different from that of the normal population (unpaired *t* test), nor were there significant differences between the distribution of these centiles over time (paired *t* test). Figures 3 and 4 show the age-adjusted IQRs for the height and weight velocity of each patient. Both the mean IQR for height velocity increased significantly from −0.61

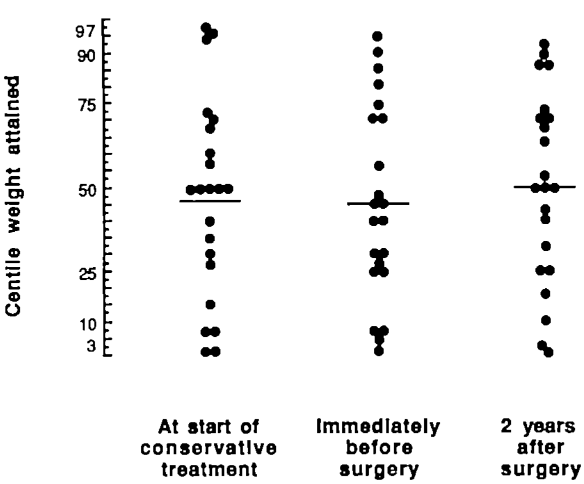

Fig. 2 Centile weights attained by 22 patients at various ages during 1 year of conservative treatment and at 2 years following subsequent surgery for primary vesicoureteric reflux.

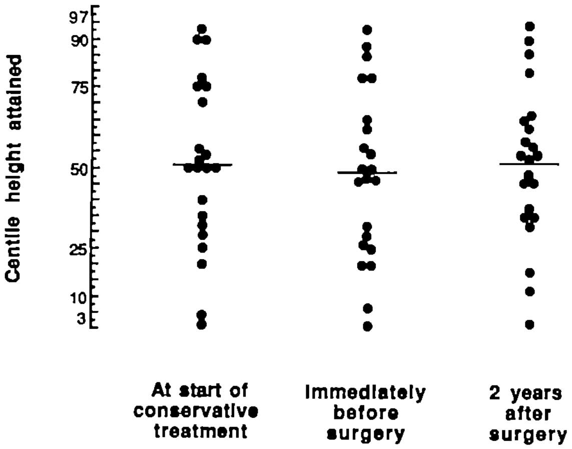

Fig. 1 Centile heights attained by 22 patients at various ages during 1 year of conservative treatment and at 2 years following subsequent surgery for primary vesicoureteric reflux.

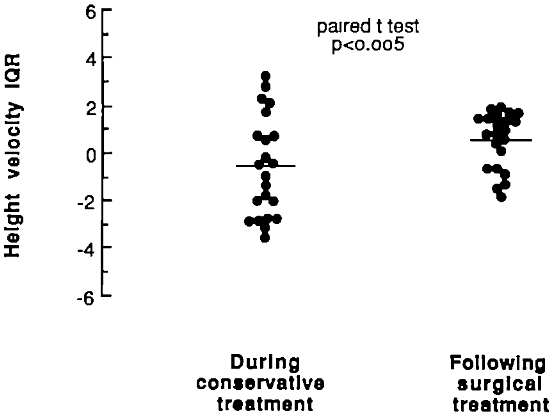

Fig. 3 Age-adjusted interquartile ratios for the height velocities of 22 patients during 1 year of conservative treatment and during the 2 years following subsequent surgery for primary vesicoureteric reflux

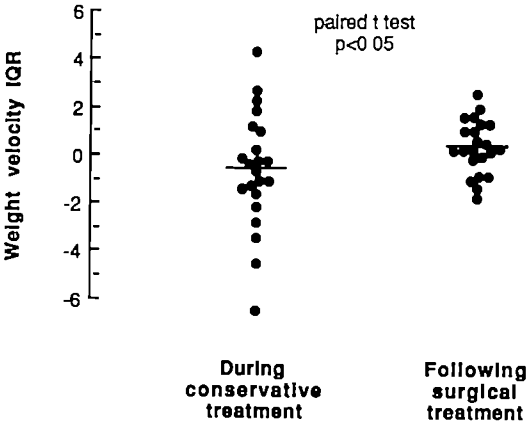

Fig. 4 Age-adjusted interquartile ratios for the weight velocities of 22 patients during 1 year of conservative treatment and during the 2 years following subsequent surgery for primary vesicoureteric reflux.

(sem = ±0.45) during conservative treatment to 0.54 (±0.25) following surgery ($P < 0.005$, paired *t* test), and the mean IQR for weight velocity increased significantly from −0.63 (±0.50) to 0.47 (±0.24) over the same period ($P < 0.05$, paired *t* test).

Discussion

Most studies of the effects of medical or surgical treatment on patients with vesicoureteric reflux have been carried out without controls for the other treatment. In this study each patient provided his or her own control, since each patient was sequentially treated, firstly by conservative or medical means, and then by surgery. As surgical treatment abolishes reflux, a cross-over design cannot be incorporated into such a study. Thus a beneficial effect of prior medical treatment on subsequent surgical treatment cannot be excluded, although such an effect would seem unlikely, since medical treatment was not associated with spontaneous resolution or regression of reflux, nor would surgery normally be undertaken until pre-existing infection had been eradicated.

The one previous report of increased physical growth after successful treatment of vesicoureteric reflux did not include control data for medical treatment (Merrell and Mowad, 1979). Unfortunately, the number of patients with primary vesicoureteric reflux was not stated, nor is it apparent whether height and weight were measured at standard times by a standard method. Furthermore, bias might have been introduced by the use of a questionnaire to ask parents for the heights and weights of their children included in the study. Thus although a marked pre-existing growth deficit was reported before surgery, and presumed catch-up growth (Tanner, 1981) recorded following surgery, these results should perhaps be approached with some caution.

In the present study the regular measurement of height and weight by trained staff using a standard technique ensured that reliable estimates were obtained, particularly of changes in height and weight over time. At the start of antimicrobial prophylaxis the mean centile height attained was nearly normal, while the mean centile weight attained was not significantly below normal. A more obvious pre-existing growth deficit might have been expected, but even a small preponderance of patients with above average growth in a sample of the size studied would have masked such a deficit. Certainly the standard errors of the mean centile heights and weights attained allow for this last possibility. However, if any pre-existing growth deficit had been large, a significant increase in the mean centile height and/or weight attained might have been expected to follow treatment.

Although the changes in growth velocity that were recorded had only small effects on both the mean centile height and weight attained, these changes provide a more sensitive and immediate measure of health than growth attained (Buckler, 1979). As the occasion of the last measurement of height and weight before ureteric reimplantation was taken as the end of the period of observed growth during conservative treatment, and also as the start of the period of observed growth following surgery, it is unlikely that any growth disturbance directly consequent upon surgery and unrelated to the cessation of reflux had any effect on the calculation of height and weight velocities. By restricting the study to the observation of growth velocity during the most stable period of growth, individual variations associated with infancy and adolescence were avoided (Tanner *et al.*, 1966; Tanner and Whitehouse, 1976), reducing inaccuracies in the method used for the age adjustment of growth velocities. The calculation of IQRs for each patient at any given age adjusted not only for the expected mean growth velocity at that age, but also for the distribution around the mean at that age. Both the age-adjusted mean IQR for height and weight velocity increased significantly following surgery above the respective means for height and weight velocity during conservative or medical treatment, suggesting that amongst this selected group of patients surgical treatment was more effective. Further follow-up data would be needed to determine subsequent growth and growth velocities, but will be complicated by adolescence in some patients.

Normal somatic growth has been reported in a group of 114 girls receiving low-dose prophylactic co-trimoxazole, amongst whom were 51 girls with vesicoureteric reflux, none of whom underwent surgical treatment (Smellie *et al.*, 1983). Although this report was not primarily concerned with patients who had vesicoureteric reflux, neither the grading nor progression of reflux was recorded, nor was data given that related only to the girls with reflux. Growth velocity rates were calculated over 6-month periods and then grouped into 1-year age groups according to the child's age at the start of the period, for calculation of standard deviation scores. In this study, growth velocity rates were calculated over the preferred 12-month interval (Buckler, 1979) and then age adjusted for the mid-point of the interval, by calculation of an IQR derived from standard data available for 3-monthly intervals (Tanner *et al.*, 1966). As the normal interquartiles for height velocity were originally calculated from standard deviations (Tanner *et al.*, 1966), the use of IQRs provided an acceptable alternative, by means of which both height and weight velocity data could be displayed in the same form.

In this study surgery was performed because of repeated breakthrough infection (6 patients) or persistence of grade III or IV reflux (16 patients). Six patients developed urinary tract infections during their *year* of medical treatment, an incidence comparable to that reported in other studies of medical treatment (Edwards *et al.*, 1977; Birmingham Reflux Study Group, 1983, 1987). Five patients developed urinary tract infections during the *2 years* following subsequent surgery, producing a difference in yearly infection rates between the 2 treatment periods which was not significant but which might partly account for the improved growth velocities following surgery. Micturating cystography demonstrated progression of the severity of reflux in 8 patients, and although the period of antibiotic prophylaxis was relatively short, this is a high number when compared to the numbers reported in other studies of medical treatment (Edwards *et al.*, 1977; Aladjem *et al.*, 1980). This high number may also partly account for the improved growth velocities following surgery. Patients with a history of abnormalities other than primary vesicoureteric reflux were excluded from this study, and thus such abnormalities cannot account for the differences in growth velocity that were observed.

Previous studies of the treatment of vesicoureteric reflux have shown that renal function can be maintained by both medical and surgical means (Birmingham Reflux Study Group, 1983, 1987; Atwell, 1984, Scott *et al.*, 1986). Renal growth has been shown to increase following surgery for vesicoureteric reflux (McRae *et al.*, 1974; Atwell *et al.*, 1978; Atwell and Cox, 1981; Ginalski *et al.*, 1986), but no significant difference in renal growth has been observed following either medical or surgical treatment when compared in a controlled trial (Birmingham Reflux Study Group, 1983, 1987). It is interesting to note, however, that in this trial there was a trend for the renal standard deviation scores to fall further during medical treatment than following surgical treatment. Although no significant differences were found between treatments within the various age groups studied, the illustration given in the most recent report (Birmingham Reflux Study Group, 1987) suggests that there might have been such a difference between treatments with all age groups combined. Amongst the patients excluded from this trial were those who failed to comply with the study protocol, the exact number of whom was not stated (Birmingham Reflux Study Group, 1983). Compliance is probably more critical to the success of medical than surgical treatment, and when compliance is poor, perhaps because of social problems, patients who are treated medically are more likely to suffer development or progression of renal scarring (Smellie *et al.*, 1985). Indeed the results of medical treatment for severe vesicoureteric reflux have not always been encouraging (Dunn and Smith, 1982), although antimicrobial prophylaxis appears to be effective in most patients with primary vesicoureteric reflux (Edwards *et al.*, 1977; Aladjem *et al.*, 1980; Birmingham Reflux Study Group, 1983, 1987), the majority of whom undergo spontaneous resolution of their reflux.

In this study of the treatment of vesicoureteric reflux a modest but significant increase in height and weight velocity were noted during the 2 years following surgery when compared with that noted during the preceding year of medical treatment. The patients studied probably represent a small sub-group of patients whose clinical progress is poor during antimicrobial prophylaxis. These results suggest that in patients with severe primary vesicoureteric reflux who fail to respond to a trial of antimicrobial prophylaxis, surgical treatment is preferable to continued medical treatment.

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Invasive Bladder Cancer. Prognostic Factors and Results of Radiotherapy with and without Cystectomy

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Summary—We report the results and complications of treatment in 205 patients with non-metastatic invasive bladder cancer. Between 1977 and 1982 there were 3 treatment groups: palliative radiotherapy, radical radiotherapy, and pre-operative radiotherapy followed by total cystectomy. Data were complete on each patient until the end of 1985 (minimum follow-up 3 years, median 5.6), when 48 patients were alive without evidence of bladder cancer and 28 had died of intercurrent illness (without clinical evidence of bladder cancer). The overall actuarial 5-year survival rate (death from any cause) was 24%. The 5-year survival rates were 13% for group 1, 25% for group 2 and 38% for group 3. Group 1 patients had a significantly shorter survival. The difference between groups 2 and 3 was not statistically significant. The prognostic factors of significance for survival were clinical stage and ureteric obstruction. Factors such as age, tumour grade and multiplicity were significant when examined singly but not in a multivariate analysis which included stage and ureteric obstruction. The actuarial incidence of all radiotherapy complications in bladder and bowel was 9.4 and 10.5% respectively.

Treatment for invasive bladder cancer includes radical radiotherapy (Goffinet *et al.*, 1975; Abratt *et al.*, 1983; Corcoran *et al.*, 1985; Edsmyr *et al.*, 1985; Fossa *et al.*, 1985, Shipley *et al.*, 1985; Yu *et al.*, 1985), salvage cystectomy in selected cases of local failure (Blandy *et al.*, 1980; Freiha and Faysal, 1983), radical cystectomy alone (Montie *et al.*, 1984; Skinner and Lieskovsky, 1984; Ghoneim *et al.*, 1985), combined pre-operative radiotherapy and radical cystectomy (Miller, 1977; Werf Messing, 1979; Bloom *et al.*, 1982; Anderstrom *et al.*, 1983; Scanlon *et al.*, 1983) and "sandwich radiotherapy", consisting of both pre-operative and post-operative irradiation (Mohiuddin *et al.*, 1985).

We report the outcome of radiotherapy with and without cystectomy in a series of patients treated at the Prince of Wales Hospital with special emphasis on survival, complications and prognostic factors. We have chosen the period 1977 to 1982 because during this time chemotherapy was not part of the initial plan of management, but was adopted from 1982 onwards (Raghavan *et al.*, 1985).

Patients and Methods

From January 1977 to December 1982, 323 patients with invasive bladder cancer were referred to for radiotherapy. Of these, 205 patients had tumour confined to the pelvis with no clinical or radiological evidence of metastases (T1–4, NX, M0) and they constitute the sample analysed in this study.

All patients had histological proof of invasive bladder cancer from transurethral resection and were staged according to the TNM classification (UICC, 1974). All underwent initial intravenous urography and chest X-ray at the time of referral and further investigations (such as nuclear bone scan, abdominal CT scan and bipedal lymphangiography) were performed as indicated.

Group 1 (palliative pelvic radiotherapy). 72 patients, mostly with advanced tumours and in poor health, were not considered fit enough for radical treatment of any sort and received pelvic radiotherapy by parallel opposed fields in fractions of 1.8–2.5 Gy per day, 4 or 5 days per week, to a total of 40–50 Gy (Fig. 1).

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Group 2 (radical pelvic radiotherapy). 88 patients, considered fit for a full course of radiotherapy but unfit (or unwilling) for total cystectomy, received whole pelvis irradiation by a 4-field plan to 40–50 Gy followed by a reduced volume boost to the bladder by a 3-field plan up to 60–70 Gy in fractions of 1.8–2.5 Gy per day (Fig. 2).

Group 3 (pre-operative pelvic radiotherapy and total cystectomy). 45 patients were selected for total cystectomy. They received radiotherapy to the whole pelvis by parallel opposed fields to 40–50 Gy as in Group 1, and total cystectomy was performed 4 to 8 weeks later.

Three patients in Group 3 had pelvic doses lower

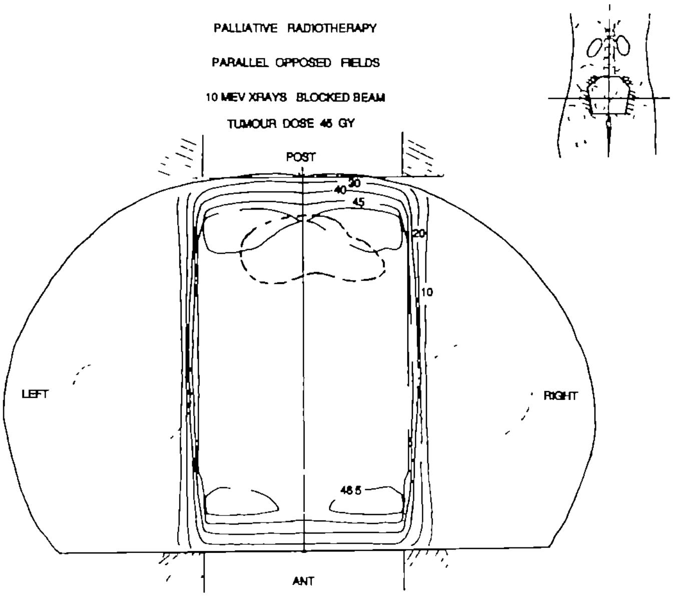

Fig. 1 Simple isodose plot of radiotherapy to whole pelvis (patient prone). 45 Gy by parallel opposed fields in palliative or pre-operative treatment Dotted lines show position of rectum and femora

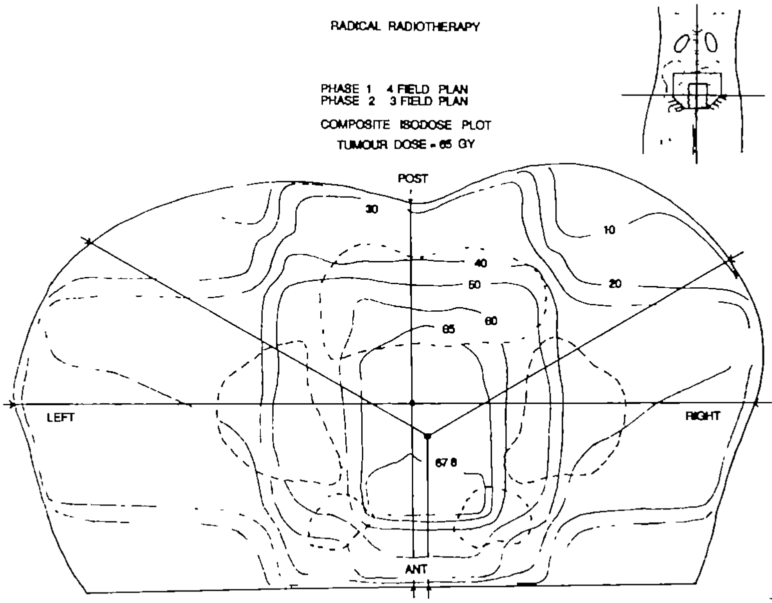

Fig. 2 Composite isodose plot of radical radiotherapy (patient prone). whole pelvis by 4 fields 50 Gy followed by bladder boost by 3 fields 15 Gy Dotted lines show position of rectum and femora

than 40 Gy (20 Gy in 5 fractions, 30 Gy in 10 fractions and 15 Gy in 5 fractions) and the cystectomy was performed within a few days of finishing radiotherapy. Only 1 patient received systemic chemotherapy (cisplatin) prior to radiotherapy. With the exception of 1 patient, who had a permanent ^{125}I seed implant of the bladder neoplasm without external beam therapy, all patients received irradiation on a 6 or 10 MV linear accelerator and all fields were treated on each treatment day. Comparison of total radiation doses, the number of fractions and overall number of days of treatment was carried out using "rets" as proposed by Ellis (1971).

During follow-up all patients had a regular physical examination and cystoscopy. The development of metastases during follow-up was assessed from symptoms, clinical findings and results of such investigations as were clinically indicated. Salvage cystectomy was performed, when appropriate, for local recurrence or persistence of bladder cancer (9 cases) or bladder complications (1 case). Complications in the pelvic organs following radiotherapy or surgery or both were scored as major (requiring surgical intervention) or minor (amenable to conservative management). Survival was calculated from the first day of radiotherapy. The cause of death was verified from hospital records and from the New South Wales Registry of Births and Deaths. When the cause of death was clearly an intercurrent illness with no evidence of bladder cancer, it was recorded as such; otherwise the cause of death was recorded as bladder cancer. Only 1 patient was lost to follow-up. Because this patient had bladder cancer and a poor prognosis at that time, she has been recorded as dead from bladder cancer on the date of last contact for the purpose of these analyses.

Data were collected on the following factors potentially prognostic for survival (assigned codes are given in brackets): sex, age (<65; ≥ 65 years), T stage (1; 2; 3, 4; X), previous intravesical therapy (yes; no), multiple tumours (yes; no), ureteric obstruction (yes, no), group (1; 2; 3), tumour type (transitional; adenocarcinoma; squamous carcinoma), histological grade (well; moderately; poorly differentiated), pelvic dose (<1520; ≥ 1520 rets), bladder dose (<1840; ≥ 1840 rets) and the year of therapy. The median values of rets were chosen as the cut-off points for pelvic and bladder doses.

Survival curves were calculated by the actuarial method (Kaplan and Meier, 1958) and were compared using the logrank test (Mantel, 1966). Assessment of the simultaneous effects of several factors on survival was undertaken using Cox regression (Cox, 1972) incorporating the modification suggested by Breslow (1974). All analyses of survival, unless specifically stated otherwise, refer to death from any cause; conclusions from analyses were the same whether survival to death from any cause or survival to death due to bladder cancer was compared. In order to allow for variable length of follow-up each complication rate was calculated actuarially as a cumulative rate from the start of treatment. Because this cumulative rate in each instance reached a plateau by about 4 years, the rate reported here is the maximum cumulative rate with its standard error and the year by which the plateau occurred.

Results

Table 1 shows the prognostic factors studied and the proportion of patients according to each factor. Table 2 shows the distribution by histology and

Table 1 Prognostic Factors

		No.	%
Sex	M	158	77
	F	47	23
Age (years) 68 (median)			
Range (39–93)			
Stage	T1	9	4
	T2	22	11
	T3	132	64
	T4	28	14
	TX	14	7
Previous intravesical therapy			
	No	175	85
	Yes	30	15
Multiple tumours			
	No	180	88
	Yes	25	12
Histology			
TCC		196	96
Adenocarcinoma		4	2
Squamous carcinoma		5	2
Grade			
1 = well differentiated		7	3
2 = moderately differentiated		61	30
3 = poorly differentiated		137	67
Ureteric obstruction			
	No	151	74
	Yes	54	26
Group	1	72	35
	2	88	43
	3	45	22

UICC stage for all 205 patients. Table 3 shows the distribution of patients by treatment group and stage.

Survival

The actuarial survival curves for death from any cause and death from bladder cancer for all patients are shown in Figure 3. The 5-year survival rate (death from any cause) was 23.8% (SE=3.3%); the 5-year survival rate (death from bladder cancer) was 34.6% (SE=3.7%).

When factors were examined individually, a significantly shorter survival was associated with age over 65 years ($P=0.004$) (Fig. 4), more advanced initial clinical stage ($P=0.001$) (Fig. 5), ureteric obstruction ($P=0.001$) (Fig. 6), less well differentiated tumours ($P=0.056$) and single tumours ($P=0.007$). Differences between tumour grades were due solely to the difference between well differentiated and other tumours. All 4 patients with adenocarcinoma and 5 with squamous carcinoma had died by 4 years, but their survival compared with that of patients with transitional cell carcinoma was not statistically significantly different.

Five-year survival rates for the 3 groups were: group 1 (palliative radiotherapy) 13.0% (SE=4.1%); group 2 (radical radiotherapy) 25.4% (SE=5.1%); group 3 (pre-operative radiotherapy and total cystectomy) 37.6% (SE=8.7%). There were

Table 2 Distribution by Stage and Histological Grade

	Stage					
	T1	*T2*	*T3*	*T4*	*TX*	*Total*
Grade 1	3		2		2	7
Grade 2	3	13	33	7	5	61
Grade 3	3	9	97	21	7	137
Total	9	22	132	28	14	205

Table 3 Distribution by Stage and Group

Stage	*Palliative pelvic radio-therapy*	*Radical pelvic radio-therapy*	*Pre-operative radiotherapy and cystectomy*	*Total*
T1	1	2	6	9
T2	8	10	4	22
T3	45	53	34	132
T4	16	12	0	28
TX	2	11	1	14
Total	72	88	45	205

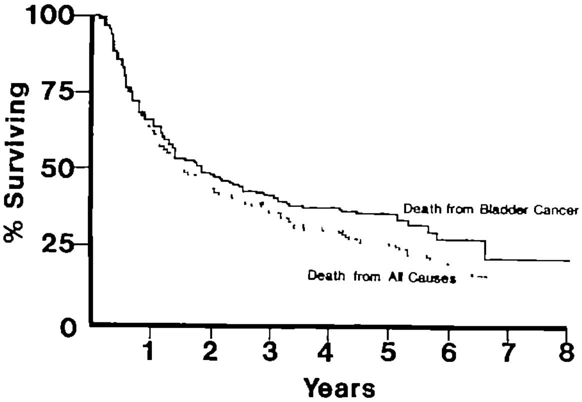

Fig. 3 Overall survival curves for death from all causes (number of deaths=157/205) and for death due to bladder cancer (129/205).

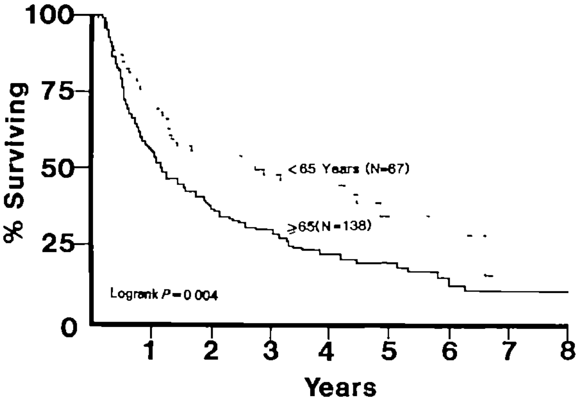

Fig. 4 Survival curves from all patients in relation to age: <65 years (number of deaths=42/67), ≥65 years (115/138).

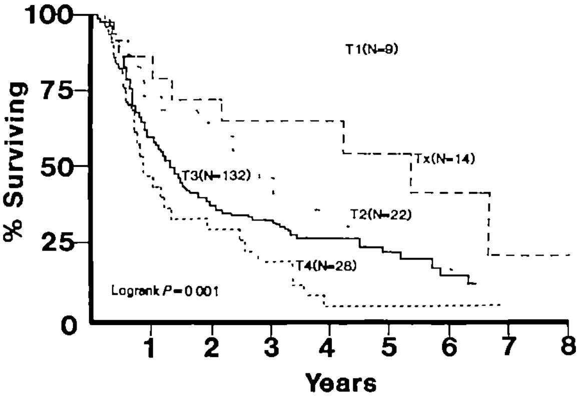

Fig. 5 Survival curves from all patients in relation to stage: T1 (number of deaths =2/9); T2 (16/22); T3 (104/132), T4 (27/28), TX (8/14). The overall logrank P value comparing 5 groups is given

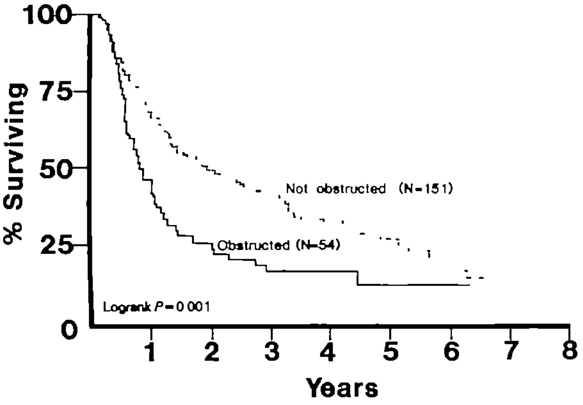

Fig. 6 Survival curve from all patients in relation to presence of ureteric obstruction not obstructed (number of deaths =111/151), obstructed (46/54)

significant differences in survival between the 3 groups (overall $P<0.001$) (Fig. 7). Survival for the palliative radiotherapy group was significantly worse than for radical radiotherapy ($P=0.008$) and for pre-operative radiotherapy and total cystectomy ($P=0.001$). Patients who underwent pre-operative radiotherapy followed by total cystectomy survived longer than those who received radical radiotherapy, but the difference was not statistically significant ($P=0.14$). Comparing groups 2 and 3, adjusted for the influence of stage by considering only the T3 cases, there was no statistically significant difference in survival ($P=0.70$) (Fig. 8).

Total radiation doses (measured in rets) to the pelvis and to the bladder were not related to survival within the narrow dose ranges examined. There was longer survival in the second half of the period (1980–1982) compared with the first half (1977–1979) (Fig. 9). This survival difference persisted after adjusting for stage and ureteric obstruction despite the lower incidence of the latter in the second half (33 versus 22%).

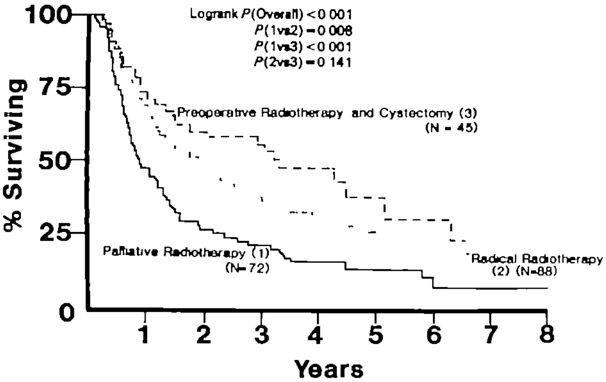

Fig. 7 Survival curves from all patients in relation to group group 1 (number of deaths =64/72), group 2 (66/88), group 3 (27/45).

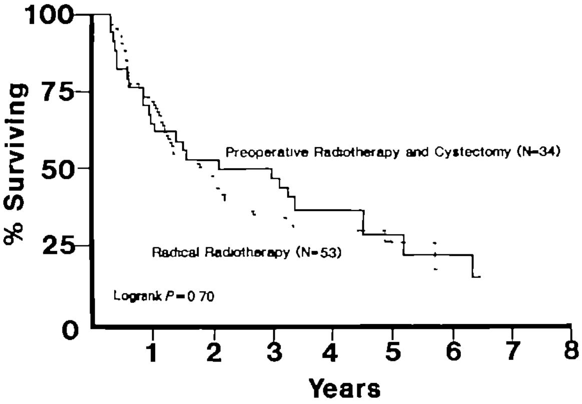

Fig. 8 Survival curves from all patients with stage T3 tumours in relation to treatment group· group 2 (number of deaths =39/53), group 3 (24/34).

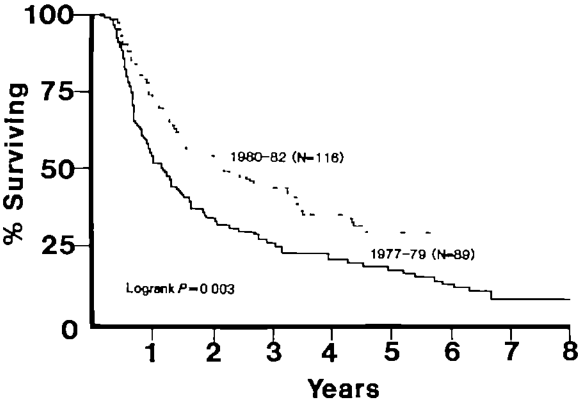

Fig. 9 Survival curves from all patients in relation to year of therapy 1977–1979 (number of deaths =81/89), 1980–1982 (76/116)

The effect of pre-operative radiotherapy on the down-staging of the tumour was assessed in 32 group 3 patients with T2 and T3 tumours (Table 4): 5-year actuarial survival was 63% when there was no identifiable cancer in the cystectomy specimen (pT0), 47% with down-staging and 0% with no stage reduction (overall $P=0.001$). This difference in survival was due entirely to the effect of any down-staging.

Cox regression analyses were performed to see which factors had independent prognostic value after allowing for imbalances of known prognostic factors between groups. Beginning with all factors which had a significant univariate effect on survival, analyses showed that only *stage* and *ureteric*

Table 4 Down-staging Effect of Pre-operative Radiotherapy

	pT0	*pT<T*	*pT=T*	*Not assessable*	*Total*
T3	11	7	10	6	34
T2	1	2	1	0	4
Total	12	9	11	6	38
5-year survival	63%	47%	0%		

P(trend) = 0.001
*p*T = pathological stage in the cystectomy specimen, T = clinical stage

obstruction had independent effects on survival. Single tumours were more likely to be associated with advanced stage and ureteric obstruction, poorly differentiated tumours with advanced stage, and older patients with more advanced stage.

Complications

Table 5 shows the distribution of complications, both major (requiring surgical treatment) and minor (responding to conservative medical treatment).

Bladder. 1 patient required salvage cystectomy for uncontrollable haematuria from telangiectasia following radical radiotherapy; 1 patient required ileal conduit diversion for a painful contracted bladder; 4 patients suffered minor bladder complications not requiring surgical intervention. Thus 6 bladder complications occurred in 160 patients treated with radiotherapy. The actuarial incidence by 4 years of all bladder complications was 9.4% (SE = 3.8%).

Bowel. 4 patients amongst 45 in the cystectomy group developed major bowel complications requiring colostomy: 3 were considered to be due to pre-operative pelvic irradiation and 1 was a surgical complication at the time of planned cystectomy; 5 patients amongst the 160 treated by radiotherapy alone had major bowel complications, an actuarial incidence by 2 years of 5.7% (SE = 2.5%), and 2 had minor bowel complications. The total number with both major and minor bowel complications attributable to radiotherapy was 10/205, an acturial incidence by 5 years of 10.5% (SE = 3.9%).

Table 5 Complications of Radiotherapy

	Major	*Minor*	*Total*
Bladder	2	4	6/160 (3.8%)
Actuarial incidence = 9.4% (SE = 3.8%) at 4 years			
Bowel	8	2	10/205 (4.9%)
Actuarial incidence = 10.5% (SE = 3.9%) at 5 years			
Other	1 (Iliac artery stenosis)	1 (Leg oedema)	

Other organs. 1 patient who had pre-operative pelvic irradiation and total cystectomy developed stenosis of an internal iliac artery requiring a vascular graft; 1 patient developed persistent moderate bilateral leg oedema following radiotherapy alone.

Discussion

The interpretation of data from retrospective series can be difficult, especially when attempting to infer the results of different treatments, because what treatment is given is determined by many factors, some of which are unknown or unrecorded. We were unable to explain the significantly longer survival in patients treated in the second half of the study (1980–1982) compared with that in the first half (1977–1979) in relation to any of the factors we recorded, although the frequent use of computerised scanning may have rendered radiotherapy more accurate in the second half. With regard to pre-treatment prognostic factors, we have confirmed the strong influence on survival of stage and ureteric obstruction (Greiner *et al.*, 1977).

Comparing our results with those of other published series, we found some similarities. Palliative radiotherapy for our patients with the poorest prognosis gave a small actuarial 5-year survival rate of 13%, compared with 4.4% in the series reported by Duncan and Quilty (1986), which included some patients with metastases. Our patients treated by radical radiotherapy had a 5-year actuarial survival rate of 25%, compared with 36% in the series reported by Duncan and Quilty (1986). We consider this difference to be due to the fact that patients with clinical stage T3 and T4 tumours constituted only half of their total study group (729/1434 = 51%), but three-quarters of ours (65-88 = 74%).

The 53 patients with stage T3 tumours managed by radical radiotherapy in our series had a 5-year actuarial survival rate of 26% which compares well with 26% reported by Duncan and Quilty (1986) and 29% reported by Bloom *et al.* (1982). It is interesting that Duncan and Quilty's patients were treated with a 3-field technique, delivering a total tumour dose of 55–57.5 Gy in 20 fractions over 4 weeks, whereas the patients of Bloom *et al.* (1982)

were treated with a technique and total radiation doses similar to ours.

In the present series, higher total radiation doses to the bladder or pelvis were not associated with a survival advantage, as suggested by Morrison (1975), but such dose response relations cannot be reliably derived from a retrospective study.

Survival after pre-operative radiotherapy and total cystectomy in our 34 patients with stage T3 tumours (29% actuarial 5-year survival) was a little lower than the 38% reported by Bloom *et al.* (1982). This may be because twice as many of Bloom's patients had salvage cystectomy (18/91 = 19.8%) compared with ours (9/88 = 10.2%).

The incidence of tumour down-staging in our 34 patients with stage T3 tumours was 18/34 (53%), which is in the range reported by other series (Table 6).

Our total actuarial rates of major radiotherapy complications in the bladder (9.4%) and bowel (10.5%) compared well with those reported by Duncan and Quilty (1986), in which only severe complications were reported. (We calculated their actuarial rates from the curves given in their publication).

The results of treating 205 patients with invasive bladder cancer at this hospital compare well with the results in other series and have been achieved with acceptably low complication rates. The pre-treatment prognostic factors of significance remain clinical stage and ureteric obstruction. Rather surprisingly, a few of the patients with a poor performance status treated by palliative radiotherapy are long-term survivors. In our series, pelvic radiotherapy followed by total cystectomy did not seem to confer a survival advantage over radical pelvic radiotherapy. Salvage cystectomy is appropriate in the management of the occasional patient who has persistent local disease in the bladder after radical radiotherapy but no clinical or scan evidence of metastases. Since uncontrolled distant metastases are responsible for the majority of cancer-related deaths, further refinements in local therapy alone would appear unhelpful in improving survival results for invasive bladder cancer. A combined multidisciplinary approach, including systemic chemotherapy and radical pelvic radiotherapy, warrants careful evaluation. Such a trial has been in progress since 1985 as an Australian multicentre randomised trial of radical radiotherapy with or without initial cisplatin chemotherapy (Raghavan, 1988).

Table 6 Down-staging of T3 Cases Following Pre-operative Pelvic Radiotherapy Assessed in the Cystectomy Specimen

Series	*Dose/Time Gy/Weeks*	*Number of patients*	*Stage reduction %*
Prout *et al.* (1973)	45/4.5	83	49
Werf Messing (1979)	40/4	89	68
Whitmore *et al.* (1977)	40/4	50	40
Bloom *et al* (1982)	40/4	74	49
Present series	45/4.5	34	53

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Intravesical Evans Bacille Calmette-Guérin in the Treatment of Carcinoma *in situ*

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Summary—We report our experience in the treatment of carcinoma *in situ* of the urinary bladder using Evans strain Bacille Calmette-Guérin (BCG). The mean period of follow-up was 30 months; 18 patients received intravesical therapy and 16 of these were evaluable. They received 8 weekly instillations of 60 mg Evans strain BCG in 50 ml of saline. No intradermal BCG was given. The response rate was 93.75% at 3 months; this declined to 57% at 2 years. The complications of therapy were frequent but mild. Seven patients failed to complete the course. These results were comparable to those obtained with other strains of Bacille Calmette-Guérin.

Urothelial carcinoma *in situ* carries a high risk of progression to muscle invasion. Its invasive potential varies between 78% for widespread primary carcinoma *in situ* (Riddle *et al.*, 1976) and 80% when this is associated with superficial transitional cell tumour (Althausen *et al.*, 1976). Since the introduction of intravesical Bacille Calmette-Guérin (Morales *et al.*, 1976) and its application to the treatment of carcinoma *in situ*, the risk of progression has decreased to 7% (Catalona *et al.*, 1987).

Response rates to intravesical BCG vary between 53 (Schellhammer *et al.*, 1986) and 100% (Brosman, 1985). This variation is due to several factors, including the use of different therapeutic schedules and different BCG strains. The strains available include Armand-Frappier (Schellhammer *et al.*, 1986), Tice (de Kernion *et al.*, 1985) and Pasteur (Kavoussi *et al.*, 1988), all of which have proven efficacy in the treatment of carcinoma *in situ* (cis). Evans BCG, despite its reported efficacy in the treatment of superficial bladder tumour (Robinson *et al.*, 1980; Kaisary, 1987), was said to be inadequate in the treatment of superficial tumour and indeed to reduce cell-mediated killing (Kierum *et al.*, 1985). In order to assess this further we studied the use of intravesical Evans BCG in the treatment of widespread urothelial cis.

Patients and Methods

Between October 1985 and March 1988, 18 patients (16 male and 2 female, mean age 63.3 years (range 44–80)) were studied. Follow-up varied between 3 and 32 months (mean 24).

Seventeen patients presented with cis which was primary in 9 cases and secondary in 8 (Table 1). An additional patient with widespread superficial G2 pTa tumour, which had been unresponsive to three other intravesical agents, received the same therapeutic schedule and has been included in this series for toxicity assessment only. Criteria for entry were

Table 1 Urothelial Pathology at Presentation

	No. of patients
Primary carcinoma *in situ*	9
Secondary carcinoma *in situ*	
Pathological stage and grade	
pTa G2	2
pTa G3	2
pT1 G2	1
pT1 G3	3

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based upon the cystoscopic appearance of the bladder urothelium and the results of 4 quadrant urothelial biopsies. Entry to the study required either more than 50% of the bladder urothelium to be involved or 3 of the 4 quadrant biopsies to be positive for cis.

Treatment consisted of 8 weekly instillations of Evans strain BCG, 60 mg wet weight in 50 ml of saline, retained for 2 h. This delivered between 1×10^9 and 5×10^9 colony-forming units per instillation. Intradermal BCG was not used. No prophylactic instillations were given.

Prior to therapy all patients had an intravenous urogram to exclude upper tract tumour and a chest radiograph to exclude active pulmonary tuberculosis. Patients were cystoscoped prior to entry, at 5 weeks (mid-treatment), at 10 weeks and 3-monthly thereafter for the next 2 years. The response at each cystoscopy was monitored with urine cytology and histologically with 4 quadrant urothelial biopsies. Blood was taken for routine haematological and biochemical measurement and liver function tests. In addition, a Mantoux test, using 0.1 ml of a 1:10,000 solution of purified protein derivative (PPD), was injected intradermally into the volar aspect of the forearm. The result was recorded by the patient's general practitioner between 48 and 72 h later. The result was expressed in terms of mm of erythema and mm of induration, a positive result being induration exceeding 5 mm in diameter.

Complications of the treatment are shown in Table 2. Frequency and dysuria were an almost universal feature, in keeping with series reported elsewhere (Lamm *et al.*, 1986). Of most significance was the observation that 7 patients (39%) were unable to complete the course because of the side effects. All symptoms resolved after cessation of treatment. One patient who failed to complete the course because of persistent pyrexia was treated with both prophylactic antibiotic and isoniazid for 2 days after instillation, but this was only transiently effective. Treatment was stopped after the fourth instillation and the malaise and pyrexia resolved.

Table 2 Complications of Intravesical Evans BCG

	No of patients
Frequency/nocturia	17
Dysuria	16
Haematuria	6
Arthritis	2
Pyrexia	1
Skin rash	1
Conjunctivitis	1
Penile oedema	1
Acute retention	1
Failure to complete course	7

Results

Eighteen patients received intravesical Evans BCG; 1 patient was withdrawn after 2 instillations and declined further follow-up and a second patient received the treatment for only widespread superficial tumour. These patients were excluded, leaving 16 for evaluation. The response was defined as complete when 4 quadrant biopsies and urine cytology were negative, as partial when either the urine cytology or the quadrant biopsies were positive, and as failure when progression of disease necessitated alternative treatment.

The results and follow-up are shown in the Figure.

Of those patients with partial responses, 5 progressed (1 at 6 months, 1 at 9 months, 1 at 12 and a fourth at 17 months). One patient who was classed as a partial responder after initial therapy developed a complete response by 3 months but subsequently developed invasive disease at 17 months. The sixth patient with a partial response had his tumour resected at 12 months but has persistent positive cytology despite negative quadrant biopsies and a normal intravenous urogram. Of the patients who progressed after therapy, this occurred at 6 months, 9 months (2), 12 months, and 17 months (2) (mean 11.6 months).

Two measurements were used in an attempt to obtain prognostic indicators of response to treatment. These were the presence of a granulomatous response in the biopsies and the Mantoux reaction; 15 patients developed a granulomatous response by 22 weeks; at 1 year, 4 (33%) who produced this initial response had progressed. The single patient with a negative response had a good response at 30 months.

The Mantoux reaction responses are shown in Table 3. Of the 16 evaluable patients, 14 were

Table 3 Results of Mantoux Reaction for 16 Patients

14 negative before therapy	5 (36%) non-converters 3 failed 2 responded 60% progression rate 9 (64%) converters 3 failed 6 responded 33% progression rate
2 positive before therapy	100% response (mean 20 months)

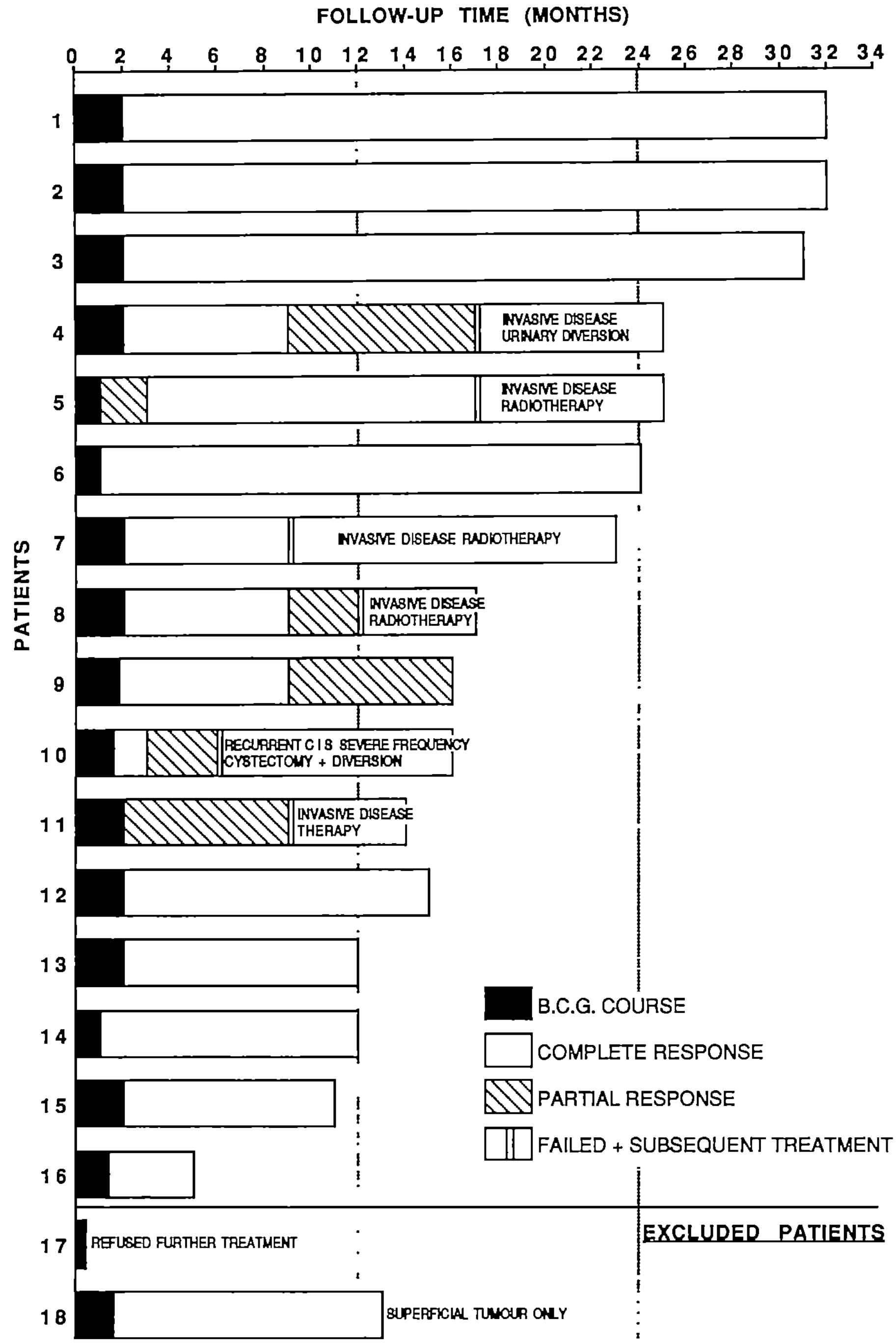

Fig. Results of treatment

negative on initial testing and 2 were PPD-sensitive. After therapy, 9/14 patients became positive. Within this group 3/9 progressed, whereas in those patients who failed to convert, 3/5 progressed ($P<0.1$, chi square test). PPD sensitivity in the converted group reverted to normal in 4 patients at a mean of 40 weeks (range 10–58) and it is perhaps of significance that all 3 patients disease progression were within this group.

Discussion

Since the introduction of intravesical BCG the prognosis of cis has improved considerably. The actuarial probability of becoming tumour-free is 77% and the probability of invasive tumour and metastases developing is 7 and 5% respectively (Catalona *et al.*, 1987). These figures are based upon one or more treatments of intravesical BCG. This wide variation in dosage schedules, strain of BCG and the use of repeated courses make comparisons between series difficult. Further difficulties arise in the definition of the response, varying from negative urine cytology and biopsies (Kavoussi *et al.*, 1988) to include those with residual papillary tumour but resolution of the cis (Herr and Pinsky, 1983).

Our results may be compared with those from other centres using a single 6-week course of BCG. BCG (Pasteur) was used in the treatment of 32 patients with carcinoma *in situ* and produced a 37% response rate at 24 months (Kavoussi *et al.*, 1988). BCG (Tice) was used in the treatment of superficial tumour for 6 weeks and yielded response rates of 41% (Soloway *et al.*, 1986) and 42% (Heney *et al.*, 1986). Our results with a response rate of 57% at 24 months compare favourably with these.

Better response rates in the treatment of cis have been reported with complete response rates of 68% at 4 years (Herr *et al.*, 1986) and 81% at 5.25 years (Brosman, 1985). However, these results are not directly comparable with those reported here, as they often represent more than one course of therapy. Brosman (1985) administered intravesical BCG until all tumour was eradicated and continued maintenance therapy twice-weekly for 3 months, then monthly for 18 months.

Prognostic indicators similar to those used in this series have not been shown to be sufficiently reliable when applied to the individual patient (Torrence *et al.*, 1988). Although a patient may respond with a positive granulomatous response and conversion of a negative to a positive Mantoux reaction (a favourable response), this does not imply a long-term response. In this series a weak PPD solution was used, whereas other workers have used an intermediate strength (1:1000) solution. Thus our results with a 1:10,000 solution, although less sensitive, may be more selective in that the non-converters had a higher proportion of the failed cases.

Although both granulomatous response and Mantoux test positivity are poor prognostic indicators, there is a need for such an indicator. It has already been shown that the normal urothelial cell population changes as a result of BCG administration (El-Demiry *et al.*, 1987) and that changes in T lymphocyte sub-sets may provide such an indicator. Recent work on the immunological response to BCG has suggested that the expression of class 2 surface major histocompatible antigen, not normally found on urothelial cells, may be an important prognostic indicator (Prescott *et al.*, 1989). A sensitive indicator is awaited, since this will not only allow the patient to be closely monitored after therapy, giving an early indication for further treatment, but will also allow a better titration of the therapeutic dose against side effects.

The intention of this study was to evaluate BCG (Evans) for patients with widespread cis. The diagnosis of cis was based on the histopathological extent of quadrant mucosal biopsies and urine cytology. All specimens were examined by one pathologist and the specimens were also reviewed at a weekly urology/pathology bladder cancer meeting. The criteria used in the diagnosis of cis in this unit have been described by Webb (1985). The use of this definition, plus regular pathological review meetings, produce a consistent pathological diagnosis. Nevertheless, the value of mucosal biopsies has recently been questioned in a multicentre study under the auspices of the Medical Research Council, where biopsy material was reviewed by 6 different pathologists on 2 separate occasions and the discrepancy was such that no useful information was forthcoming (Richards *et al.*, 1989). In view of the apparent difficulty that pathologists have in making the diagnosis of cis, it could be argued that some of the patients in this study did not require treatment at all. However, some of our patients with widespread cis, as diagnosed by our pathologists, later developed invasive tumour despite BCG therapy and this was also true when the original diagnosis was primary cis (no exophytic tumour prior to BCG therapy). Previous work has also shown that dysplasia or cis, as reported in our department, will predict those patients liable to develop recurrent tumour (Smith *et al.*, 1983). For these reasons we assumed that the diagnosis of cis was valid when used in this report. There is, however, a need for consensus amongst pathologists about the mucosal biopsy findings and we feel that regular pathology review sessions are a step towards this.

Our results suggest that the Evans strain of BCG is as effective as other strains in the treatment of carcinoma *in situ*. Primary carcinoma *in situ* is relatively uncommon and it will require a larger study to define prognostic factors and further studies to determine the optimum instillation regimen. The protocol used in this study has been used by several other centres and the larger series will be reported in due course. Further multi-centre studies are planned to determine the optimum treatment regimen.

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HLA–DR Expression by High Grade Superficial Bladder Cancer Treated with BCG

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Summary—The local immune response to intravesical BCG therapy for widespread carcinoma *in situ* and superficial bladder tumour was assessed using immunohistochemical methods on serial biopsies obtained during treatment. The main findings were the induction of a strong level of HLA–DR expression by urothelial cells which persisted for several months after completion of therapy. This coincided with a mononuclear cell infiltrate in the bladder wall consisting predominantly of activated helper T lymphocytes. Smaller numbers of macrophages, suppressor cytotoxic T lymphocytes and B lymphocytes were also found. These new findings confirm that the inflammatory response to BCG involves the urothelium in an immunological reaction and suggest that the success of immunotherapy with intravesical BCG may be due to enhanced tumour antigen recognition.

Bacillus Calmette-Guérin (BCG) is currently the most effective intravesical agent for the treatment of superficial bladder cancer and particularly for carcinoma *in situ* (CIS), with complete response rates of 80% (Lamm, 1987) for a lesion which is otherwise very difficult to treat and carries a 57% mortality rate at 5 years (Utz *et al.*, 1970). However, the mechanism of anti-tumour activity of BCG remains unclear, although the available evidence suggests that this is immunological in nature.

Successful therapy depends on an intact host cellular immune system; congenitally T lymphocyte deficient (nude) mice with transplanted bladder tumours fail to respond to intravesical BCG until they are given T lymphocytes (Ratliff *et al.*, 1987). The success of therapy also correlates with the development of a delayed type hypersensitivity response to intradermal purified protein derivative (PPD) (Kelley *et al.*, 1985) and the appearance of circulating antibodies to BCG (Lamm *et al.*, 1981). Although these latter parameters are measurements of the systemic immune response to BCG, its anti-tumour action is essentially local, with direct contact between vaccine and tumour being required for effective tumour cell killing (Zbar and Tanaka, 1971).

Despite this knowledge that local mechanisms are involved, little information has been obtained about the *in vivo* local immune response. Guinan *et al.* (1986) reported that intravesical BCG administration in the normal rat bladder resulted in a significant increase in T lymphocyte infiltration compared with bladders treated with thiotepa. A further indication that T lymphocytes are involved in the local response is the sharp rise in the urinary level of interleukin-2, a lymphokine released by activated helper T lymphocytes, following intravesical BCG administration in humans (Haaff *et al.*, 1987).

We have therefore investigated the local immune response to BCG in the bladder wall by immunohistochemical analysis of serial biopsies from patients undergoing a course of this treatment. These were high-risk patients with extensive carcinoma *in situ* and/or superficial tumour who would otherwise have been offered cystectomy.

A preliminary immunohistochemical analysis of an earlier group of 7 patients has been published previously (El-Demiry *et al.*, 1987). We have further

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investigated this phenomenon and present a more detailed analysis of a further 10 patients.

Patients and Methods

The series comprised 9 patients (age range 44–80 years, mean 62.4) with CIS involving more than 50% of the bladder surface area and 1 female patient aged 55 years with widespread recurrent intermediate grade superficial transitional cell carcinoma (G2pTa) which had failed to respond to other intravesical chemotherapeutic agents. Five of the CIS patients also had associated high grade superficial (Ta or T1) tumour prior to treatment.

These patients were all treated in one centre but they form part of a Scottish Urological Group Trial of BCG therapy. Briefly, the protocol is a standardised course of investigation which includes cytoscopy with histological and urinary cytological assessment prior to treatment, between the fourth and fifth instillation, 2 weeks after completion of therapy and then 3-monthly for 2 years.

BCG therapy

Evans BCG (Glaxo Danish Strain) was obtained as a lyophilised preparation; 60 mg wet weight of this preparation containing 1–5 × 10^9 colony forming units of BCG were suspended in 60 ml of saline and instilled into the bladder via a urethral catheter which was then removed. Patients were instructed to retain the BCG solution for 2 h if possible. The instillation of BCG was repeated weekly for 8 weeks.

Bladder biopsies

Four quadrant "cold cup" biopsies and biopsies of any abnormality were taken at every cystoscopy for routine histopathology and a further 2 similar biopsies were snap frozen in liquid nitrogen for immunohistochemical analysis. Samples were then stored at −70°C until cryostat sections 5 to 10 µm thick were cut, air dried and fixed in acetone. They were than either stained immediately or stored dehydrated in aluminium foil at −20°C until used.

The following controls were used:

(1) Normal bladder biopsies from multi-organ transplant donors.
(2) Post-instillation biopsy from 2 patients who had undergone intravesical Mitomycin C therapy 8 weeks previously.
(3) Chronically inflamed bladder biopsies from bladder cancer patients which showed radiation cystitis, follicular cystitis or non-specific chronic inflammation on microscopy.

Immunohistochemical staining technique

For this study we used a streptavidin-biotin immunoalkaline phosphatase technique. In summary, this consisted of:

(i) Returning the stored slides to room temperature and washing with 0.2 M Tris buffered saline (TBS) pH 7.6 for 5 min.
(ii) Incubation of sections with 25% normal rabbit serum (NRS) in TBS for 10 min.
(iii) Removal of excess 25% NRS and incubation with optimal dilution of murine monoclonal antibody (Table 1) in 2% NRS for 60 to 90 min.
(iv) Washing section with TBS and incubation with biotin-linked goat anti-mouse immunoglobulin * for 30 min.
(v) Washing section with TBS and incubation with streptavidin linked alkaline phosphatase * for 30 min.
(vi) Sections stained with a Fast Red TR/Naphthol AS–MX phosphate substrate (5 mg and 2 mg) in 10 ml of veronal acetate buffer pH 9.2 containing 400 µl of a 1.2% solution of levamisole in distilled water to block endogenous alkaline phosphatase activity.
(vii) Counterstain lightly with Mayers haematoxylin and mount section in neutral glycerine jelly.

Table 1 Monoclonal Antibodies

Major histocompatibility antigens (framework)	
Anti-HLA-ABC	M736*
Anti-HLA-DR	DA6 231†
T lymphocytes	
Pan-T lymphocyte	Leu 4‡
T helper subset (T4)	M716* (CD4)
T suppressor/cytotoxic (T8)	M707* (CD8)
Interleukin-2 receptor	M731*
B lymphocytes	
Pan B lymphocyte	M708* (CD22)
Macrophage	
Pan-macrophage	M718*
Natural killer cell	
HNK-1	Leu 7‡
IgFc receptor	Leu 11b‡
Interdigitating/dendritic cell	
Langerhans/dendritic cells (T6)	M721* (CD1)

* = Dakopatts Ltd
† = Dr K. Guy, MRC, Edinburgh.
‡ = Becton Dickinson Ltd

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* Immu-mark staining kit, ICN Pharmaceutical

Assessment of results

Biopsies were examined by light microscopy by two observers (S.P. and A.B.). All cell counts were made at × 320 magnification and all figures quoted referred to cells/high power field (HPF)—area = 0.07 mm^2. Results were expressed both semiquantitatively and in the case of T lymphocyte parameters also quantitatively.

Results

Routine histology

Three patients failed to complete the course of BCG (4, 4 and 5 instillations); 1 patient required cystectomy for persistent CIS but in the other 8 cases there has been no recurrence of CIS (mean follow-up 9.4 months). However, 3 of these patients have developed discrete high grade tumour recurrences (G3pTa 3 months, G1pT1 9 months, G3pT1 1 year after completion of therapy). The patient with extensive recurrent papillary tumour before treatment remains free of tumour 12 months after therapy.

Routine H and E staining of bladder mucosal biopsies showed that all 10 patients developed a marked round cell inflammatory response with typical non-caseating epithelioid granulomas and sloughing of urothelial cells. In all cases except 1 these granulomas had disappeared by 6 months after therapy together with the majority of the inflammatory infiltrate.

Immunohistochemistry

The results of immunohistochemical analysis are summarised in Tables 2 and 3. Stained sections omitting primary monoclonal antibodies showed no non-specific staining.

Table 3 T Cells in the Submucosa

		Neoplastic bladder biopsies	
	Normal bladder	*Before treatment*	*After BCG treatment*
Subset analysis mean T4.T8 ratio	0.68	4.96	3 13
Mean interleukin-2 receptor expression	—	9%	28.2%
Class II MHC* (HLA–DR) expression	—	+	++

* Not expressed quantitatively because of other cell types also expressing this antigen

In all 10 cases, BCG treatment induced strong uniform expression of HLA–DR antigen by the urothelial cells (Figs 1–4). This was usually as intense as (or more intense than) the expression of similar epitopes by macrophages in these biopsies. In 5 of 8 biopsies examined 3 months after completion of therapy the urothelium was still uniformly strongly positive; the remaining 3 cases were patchily positive. At 6 months after therapy the figures were 3 positive, 2 patchily positive and 3 negative. HLA–DR antigen was not expressed by the CIS in the cystectomy specimen or by any of the recurrent tumours.

The predominant cell in the mononuclear cell infiltrate was the T lymphocyte. In addition to infiltrating the urothelium, these cells formed the bulk of suburothelial cellular aggregates found in

Table 2 Semiquantitative Analysis of MHC Antigen Expression by Urothelium and Mononuclear Cell Infiltration in Study Groups

	Normal bladder	*Before treatment*	*Bladder tumour patients*		
			BCG treatment	*After Mitomycin C*	*Chronic inflammation*
Urothelial cells					
HLA-ABC	++	+ or +/−	++	++	++
HLA-DR	−	− or +/−	++	−	− or +/−
− not expressed, +/− patchy expression, + weak expression, ++ strong expression					
Infiltrate					
T cell	+	++	++++	+	
B cell	−	+	++	−	
Macrophage	+	++	+++	+	Variable
NK cell	−/+	+/−	+/−	+/−	
Dendritic/ID cell	+	+	+	+	
Predominant site	Epithelium	Submucosa	Submucosa	Submucosa	Submucosa
− range + to ++++ (normal to intense infiltration)					

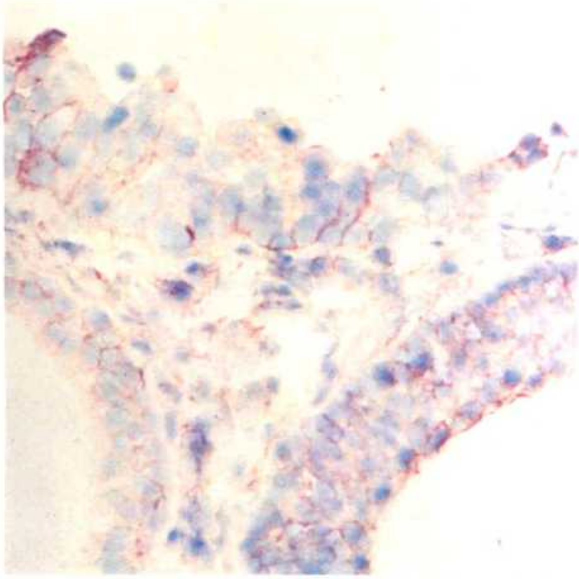

Fig. 1 Before BCG treatment. HLA–ABC × 360. Urothelium showing the changes of carcinoma *in situ* (top) overlying von Brunn's nests. The cell membranes of all urothelial cells stain positively for this antigen.

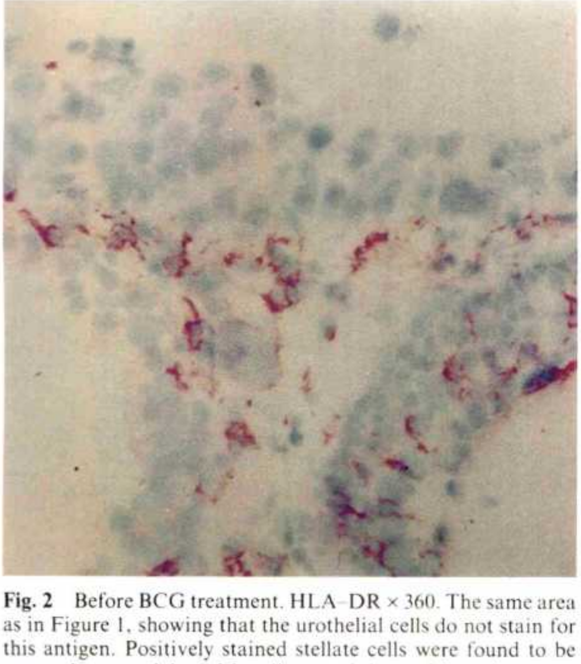

Fig. 2 Before BCG treatment. HLA–DR × 360. The same area as in Figure 1, showing that the urothelial cells do not stain for this antigen. Positively stained stellate cells were found to be macrophages and dendritic cells on staining serial sections.

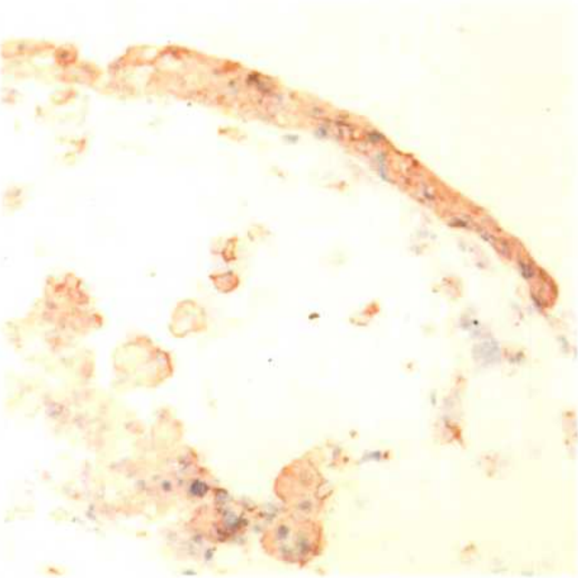

Fig. 3 After BCG treatment. HLA–DR × 240. Section of bladder biopsy taken at the end of treatment. The urothelium (top) is still morphologically carcinoma *in situ* but has become strongly HLA–DR positive. The submucosa contains numerous multinucleate HLA–DR positive cells which may be Langhans giant cell precursors.

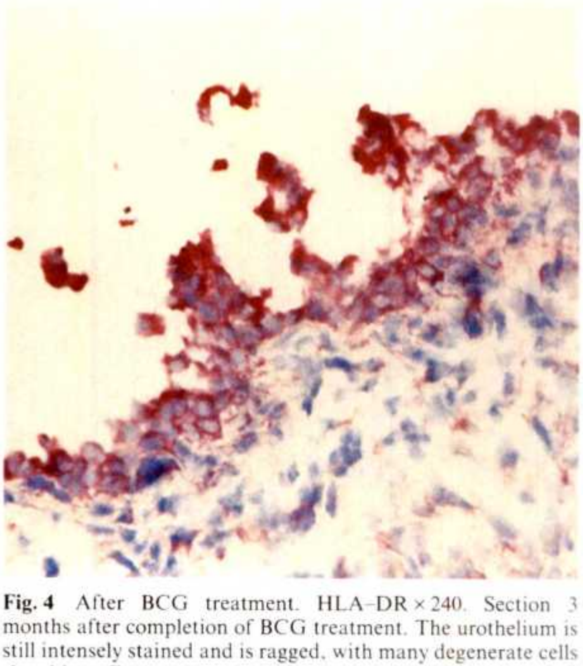

Fig. 4 After BCG treatment. HLA–DR × 240. Section 3 months after completion of BCG treatment. The urothelium is still intensely stained and is ragged, with many degenerate cells sloughing off.

both treated and untreated bladders and were the main constituent cell of the peripheral cuffs of granulomas. The submucosal T cell infiltration in normal bladders (mean 1.36, range 1.1–1.64 cells/HPF) was increased in the untreated neoplastic biopsies (mean 38.8, range 3.2–101 cells/HPF). Measurement of the T cell infiltrate between the aggregates and granulomas showed a further increase after BCG therapy (mean 139, range 64–272 cells/HPF) which was declining by 6 months after treatment (mean 81.3, range 2.3–259 cells/HPF). Further T cell analysis (Table 3) showed that unlike the findings in normal bladder, the vast majority of these cells were of the helper (T4) variety and that by their expression of interleukin-2 receptors and HLA–DR many of these were in an immunologically active state. This activation was increased by BCG. The excess of helper T cells began to decline 6 months after treatment when the mean T4:T8 ratio fell to 1.16 (range 0.5–1.98).

Macrophages and B lymphocytes formed the bulk of the remainder of the cellular infiltrate. The macrophages were widespread, scattered throughout the epithelium with T cells and throughout the lamina propria as well as being intimately involved with T cells in suburothelial aggregates and granulomas. B lymphocytes were almost exclusively confined to germinal follicles in the lamina propria.

Discussion

The most striking finding of this study was the intense expression of HLA–DR antigen by urothelial cells in all patients treated with BCG therapy. This confirms and extends our earlier results (El-Demiry *et al.*, 1987). We have shown that this antigen expression is apparent after 4 weeks of treatment and persists for at least 3 months after completion of treatment, with the majority of biopsies showing at least patchy expression at 6 months. The time course of the "aberrant" expression of HLA–DR antigen by urothelium coincides with a mononuclear cell infiltrate in bladder mucosa which consists predominantly of T lymphocytes, although there are increased numbers of all immune cell types over normal. The helper subset form the bulk of the T lymphocyte infiltrate and increased expression of interleukin-2 receptors and HLA–DR antigen by these cells suggests that they are immunologically active. This confirms the previous report by Haaf *et al.* (1987), which showed that the urinary levels of inlerleukin-2, a lymphokine released by activated helper T lymphocytes, rose sharply after intravesical BCG administration.

The expression of HLA–DR antigen by epithelial cells theoretically has major immunological implications. This antigen is normally confined to certain cells of the immune system including macrophages, B lymphocytes and activated T lymphocytes and also vascular endothelium and a few areas of epithelium, *e.g.* tongue and urethra (Daar *et al.*, 1984). Expression of HLA–DR is required for any cell to interact with helper T lymphocytes and thus to act as an antigen presenting cell. Restriction of HLA–DR to a few cell types has therefore been proposed as the major defence against autoimmune disease (Mason, 1985). Conversely, "aberrant" HLA–DR expression by epithelial cells has been found to be associated with autoimmune conditions such as Hashimoto's thyroiditis, where the stimulus for initial expression may be viral (Bottazo *et al.*, 1983). However, "aberrant" expression is also found in the absence of demonstrable autoimmune disease in inflammatory conditions associated with a T lymphocyte infiltrate such as gastritis (Spencer *et al.*, 1983) and the late skin tuberculin reaction (Scheynius and Tjernlund, 1984) and less strongly by some cells within solid tumours (Durrant *et al.*, 1987). This has suggested that some such expression may simply be due to exposure to a factor or factors released by T lymphoctyes. The most likely candidate is interferongamma, another lymphokine released by activated helper T lymphocytes which has been shown to induce HLA–DR expression by several cell types *in vitro* (Basham and Merrigan, 1983). Little is known about the conditions which may induce HLA–DR expression by urothelium which under normal conditions is HLA–DR negative (El-Demiry *et al.*, 1986).

In this report we have shown that chronic inflammatory conditions in bladder cancer patients such as follicular cystitis and radiation cystitis and Mitomycin C instillation are not associated with "aberrant" HLA–DR expression. We have also found that approximately one-third of superficial (Ta or T1) bladder tumours will express HLA–DR antigen, but usually only weakly and patchily, and the remainder of superficial lesions and nearly all muscle-invasive tumours were HLA–DR negative (unpublished observations). This may be as a response to the heightened interferon—gamma production by the mononuclear cells of bladder cancer patients (Shapiro *et al.*, 1984).

"Aberrant" expression of HLA–DR by neoplastic urothelial cells may simply be a bystander effect of exposure of these cells to interferon released by the BCG activated helper T lymphocytes, but by its intensity and persistence it is hard to believe that this would not affect tumour antigen recognition by T lymphocytes. Supportive evidence comes from work by Guerry *et al.* (1984), who showed that HLA–DR positive malignant melanoma cell lines taken from early disease will stimulate autologous lymphoproliferative responses *in vitro* and that the use of anti-HLA–DR serum blocks this effect. If this were the mode of action of BCG it would also explain why the anti-tumour effects can be transferred from one experimental animal to another by BCG-stimulated splenocytes bearing the helper T cell phenotype in the absence of transfer of any other cell type or BCG organism (Davies and Sabbadini, 1982).

As for the final mediators of tumour cell destruction, cytotoxic T lymphocytes, macrophages and B lymphocytes were present in relatively large numbers. There is some evidence that BCG-stimulated monocytes may release increased amounts of a cytolytic factor which promotes tumour cell lysis (Nakamura *et al.*, 1987). Natural killer cells have been proposed as the mediators of BCG anti-tumour activity (Pang and Morales, 1982) but they were scanty in the biopsies we examined, which suggests that their role is relatively unimportant.

In summary, we have shown that intravesical BCG therapy induces intense "aberrant" expression of HLA–DR antigen by neoplastic urothelial cells and that this change is associated with infiltration of the bladder mucosa by activated helper T lymphocytes. We therefore propose that a possible anti-tumour mechanism of BCG therapy may be via an enhanced immunological recognition of tumour in a similar process to autoimmune disease.

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Scanning Electron Microscopic Findings in Interstitial Cystitis

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Summary—Scanning electron microscopy (SEM) was performed on transurethral resection biopsies from 13 patients with classic interstitial cystitis. Biopsies from 9 patients with stress incontinence served as controls. The SEM appearance of the bladder surface in interstitial cystitis varied considerably, exhibiting small round and large polygonal cells. The proportion of cells displaying round uniform and pleomorphic microvilli was high and sometimes dominated the area examined. SEM characteristics earlier assigned to bladder tumours were detected in patients with interstitial cystitis and, at a lower frequency, also in control patients. The mucin layer covering the urothelial cells seemed reduced in interstitial cystitis compared with control specimens. Surface characteristics specific for interstitial cystitis were, however, not detected by SEM.

Scanning electron microscopy has been used to assess the surface characteristics of urinary tract tumours and in urinary tract infection in humans and in experimental rat models (Jacobs *et al.*, 1976, 1977; Kjaeregaard *et al.*, 1977; Price *et al.*, 1980; Jacobs *et al.*, 1981; Smith, 1982; Elliott *et al.*, 1984). In a recent study of normal, neoplastic and inflamed human bladder mucosa it was considered possible to differentiate between neoplastic and inflammatory urothelium except in cases of extremely severe cystitis (Herd and Williams, 1984).

The aetiology of interstitial cystitis is not known, but attention has been focused on the possibility that an increase in the permeability of the urothelium might be an aetiological factor. Thus Parsons *et al.* (1983) suggested that defects in the glycosaminoglycan layer may permit toxic substances present in the urine to penetrate the bladder wall and that this would be of aetiological significance in interstitial cystitis.

The present SEM study was performed to evaluate the surface characteristics in interstitial cystitis and to compare these with the findings in patients with stress urinary incontinence as well as with the findings earlier reported in patients with urinary tract tumours and in those with polypoid cystitis.

Patients and Methods

Biopsy specimens were taken from 13 patients with clinical symptoms and cystoscopic and light microscopic signs of classic interstitial cystitis. Light microscopic examination revealed urothelial detachment, mucosal ulcerations, oedema of the lamina propria and a mixed inflammatory infiltration along with perineural and perivascular infiltrates of lymphocytes. Mucosal mast cells in the lamina propria and connective tissue mast cells present in the muscular layer were markedly increased (Fig. 1).

All patients with interstitial cystitis had urinary frequency and chronic suprapubic pain relieved by voiding. The duration of symptoms was more than 1 year and the mean age was 62 years (range 30–86); 11 patients were female and 2 were male. Transurethral resection biopsies from 9 female patients investigated because of stress urinary

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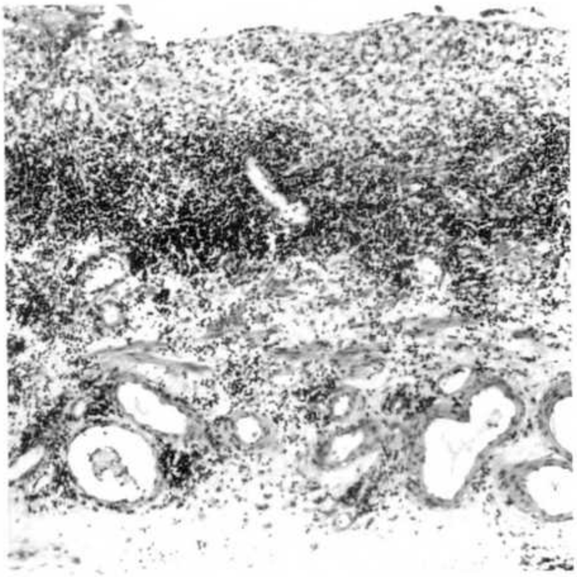

Fig. 1 Bladder biopsy of patient with interstitial cystitis showing mucosal ulceration, oedema and extensive chronic inflammation. (H and E ×60).

incontinence were obtained after oral and written consent. Their mean age was 55 years (range 35–73). Light microscopic examination revealed no noteworthy pathological changes.

All specimens were obtained during cystoscopy using Cystosol as the irrigating solution. The biopsies obtained from ulcerated areas, as well as from normal appearing bladder mucosa, were immediately divided into two portions. One portion was fixed in 4% buffered formaldehyde or in an iso-osmotic mixture of 0.6% formaldehyde and 0.5% acetic acid (IFAA). These specimens were embedded in paraffin and 5 micron sections stained with haematoxylin and eosin, Weigert van Gieson, and with toluidine blue. The specimens for SEM examination were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.2 at room temperature and were post-fixed in 1% osmium tetroxide. They were rinsed in buffer and processed through a series of graded ethanol, transferred into amylacetate and dried in a critical point equipment. The specimens were then mounted on holders, coated with gold and examined by a JEOL 100 CX electron microscope.

The cell types were classified according to the system proposed by Jacobs *et al.* (1981). The proportion of cells exhibiting surface changes were roughly estimated as follows: absent, scarce (<5%), moderately frequent (5–30%) and frequent (>30%).

Results

Control specimens

SEM examination demonstrated that the superficial cells were in large areas covered by a rather amorphous layer which prevented distinct identification of the individual cells (Fig. 2). In other areas, polygonal to round cells with distinct cell borders and a rather smooth cell surface were seen. Some of the cells displayed round uniform microvilli on the luminal surface (Fig. 3). Cells covered by few to numerous round uniform microvilli, sometimes condensed at the cell margins, were also detected (Fig. 4). Occasionally, more round or polygonal cells with impaired cell to cell contact were observed. Some of these cells exhibited few to numerous pleomorphic microvilli and in small foci these cells dominated the area examined (Fig. 5). The SEM findings are summarised in the Table, which shows that type 0–III cells according to Jacobs *et al.* (1981) were present in most specimens and that type IV A and B cells were also detected in 5 of the 9 control patients. Thread-like and leafy microridges were observed on occasional cells.

Interstitial cystitis

In specimens from patients with interstitial cystitis, areas covered by a mucinous layer were present, but the areas exhibiting other surface characteristics were clearly larger than those in control specimens. The SEM appearance of luminal cells

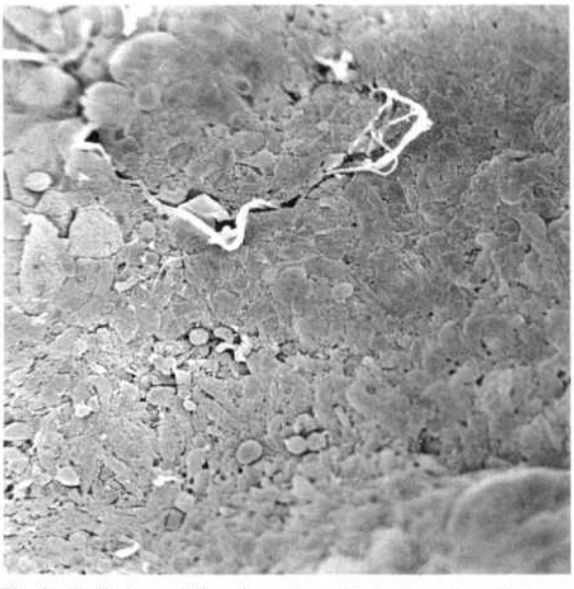

Fig. 2 Indistinct cell border and a well developed mucin layer. Control patient. (×450).

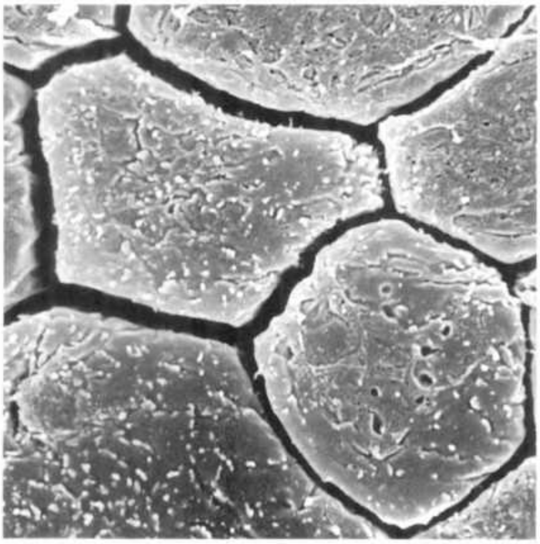

Fig. 3 Round polygonal cells with distinct cell borders and occasional round uniform microvilli. Control patient. (× 1500).

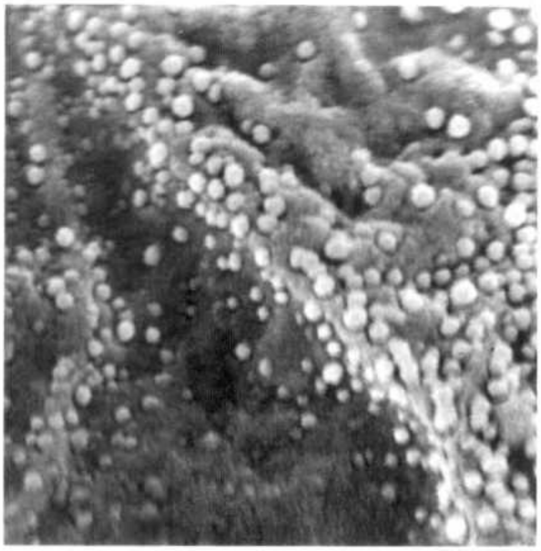

Fig. 4 Round uniform microvilli condensed at the cell borders. Control patient. (× 7500).

varied considerably in each specimen and small round and larger round to polygonal cells with few to numerous round uniform and pleomorphic microvilli were easily detected (Fig. 6). These cells appeared singly or in clusters and frequently had an impaired cell to cell contact. According to Jacobs *et al.* (1981), these cells were of type 0–III and were detected in a scarce to moderate frequency in most of the specimens. In other areas, cells covered by round uniform microvilli or with a pebbly appearance and with thick seams between cells were detected at a low frequency (Fig. 7). Only occasional

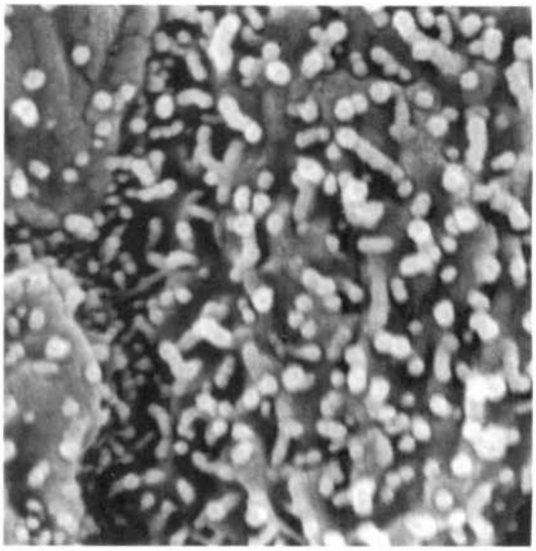

Fig. 5 Round uniform and pleomorphic microvilli. Control patient. (× 7500).

Table Correlation between Surface Characteristics according to Jacobs *et al.* (1981) and Type Lesion

Control specimens

	0	I	II	III	IV	A	B	C	D
1	F	S	S			S	S		
2	F	M	S	S		S	S		
3	F	M	S						
4	F	S	S	S					
5	F	S	S	S					
6	F	S	S	S					
7	F	M	S	S		S	S		
8	F	M	M	S		S	S		
9	F	S	S			S	S		

Interstitial cystitis

	0	I	II	III	IV	A	B	C	D
1	M	M	M	M		S	S		S
2	F	M	S	S		S	S		
3	F	M	M	M		S	S		S
4	M	M	M	F		S	S		S
5	F	S							
6	F	S	M	M					
7	F	S	S	S		M	M		
8	F	S	S	S		F	S		
9	S	S	M	M		M	M		
10	S	M	M	M					
11	M	M	M	M		S			
12	F	M	S	S		S	S		
13	M	S				S			

S = scarce (< 5%). M = moderate (5–30%).
F = frequent (> 30%).

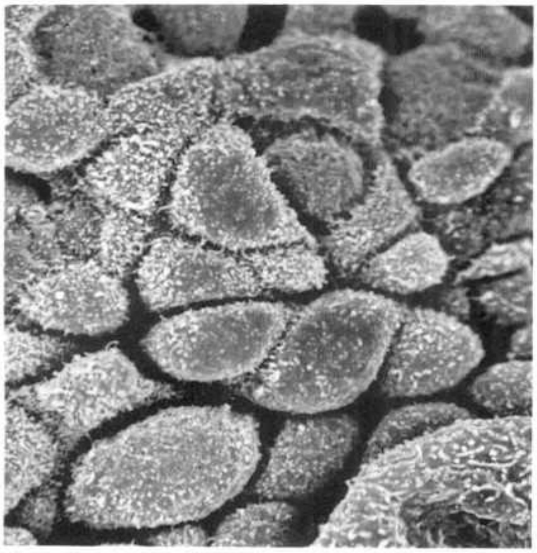

Fig. 6 Numerous round uniform and pleomorphic microvilli on cell surfaces. Interstitial cystitis. (× 1200).

cells with thick seams exhibited frequent pleomorphic microvilli on the luminal surface and thus the majority of these cells were of type IV A and B according to Jacobs *et al.* (1981). Type IV D cells were observed at a low frequency. However, no type IV C cells with pleomorphic microvilli appearing in clusters were detected. Thread-like and leafy microridges sometimes with pleomorphic microvilli on the edges were occasionally seen (Fig. 8). Branching forms of pleomorphic microvilli and microvilli with bulbous tips were identified (Fig. 9). SEM examination showed no difference in the surface characteristics of areas containing lesions and cystoscopically normal areas.

Discussion

Biopsy specimens from clinically and light microscopically normal urinary bladders are often covered by a mucinous layer that conceals the

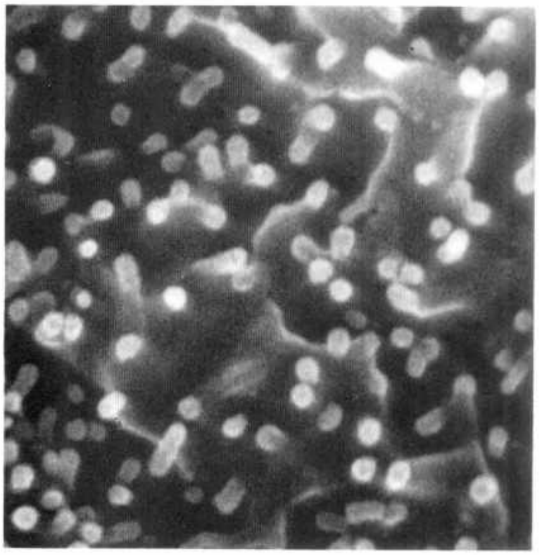

Fig. 8 Leafy ridges with round uniform microvilli and occasional pleomorphic microvilli. Interstitial cystitis. (× 15,000).

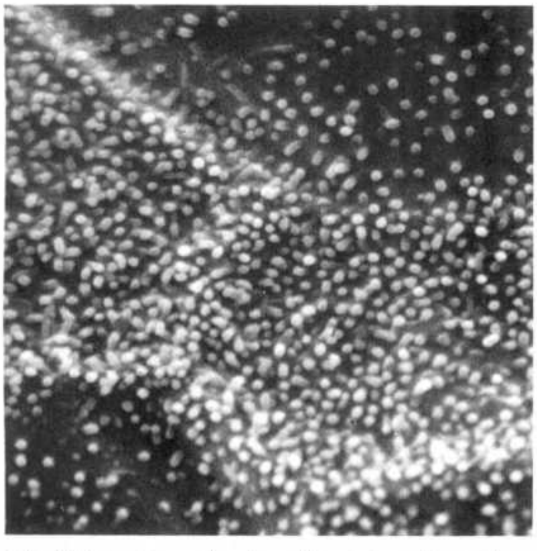

Fig. 7 Numerous round microvilli condensed at the cell borders. Interstitial cystitis. (× 7500).

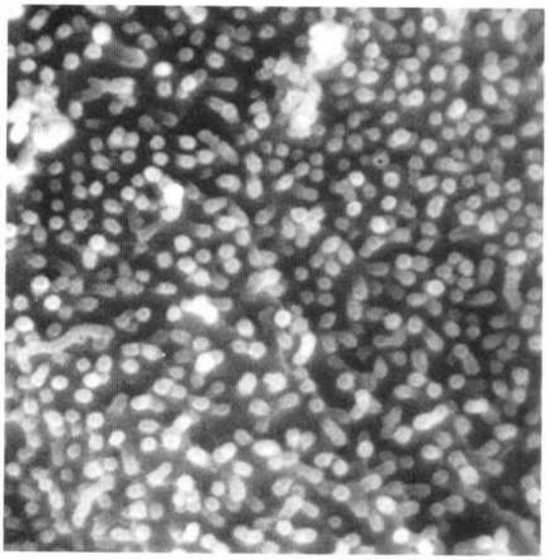

Fig. 9 Leafy ridges and pleomorphic microvilli with bulbous tips. Interstitial cystitis. (× 10,000).

underlying cell surface structures. It has been suggested that the glycocalix plays an important role in protecting the bladder from bacteriological and toxic insults (Parsons *et al.*, 1977, 1983). In acute and chronic urinary tract infections, disruptions in this layer have been observed, allowing adherence of bacteria to superficial cells (Elliott *et al.*, 1984). These cells frequently become damaged and sloughed off.

In the current study we examined biopsies from patients with interstitial cystitis and control patients by SEM. All specimens contained areas with a mucinous layer. However, the area with a disrupted or absent mucinous layer was larger in the specimens from patients with interstitial cystitis than in control specimens. Dixon *et al.* (1986), however, found no difference in the appearance, thickness and distribution of the glycocalix in their study on interstitial cystitis using transmission electron microscopy (TEM). This difference may be explained by the fact that SEM allows the examination of much larger surface areas. Furthermore, interstitial cystitis is a heterogeneous syndrome (Fall *et al.*, 1987) and the proportion of ulcer versus non-ulcer patients could affect the result. The present study was completely limited to patients with classic disease, *i.e.* focal lesions of the bladder. The defects in the mucinous layer which we observed support the suggestion by Parsons *et al.* (1983) that they are of aetiological significance in interstitial cystitis. One must bear in mind, however, that similar findings have been described in acute and chronic urinary tract infections in humans (Elliott *et al.*, 1984) and rats (Balish *et al.*, 1982) and we observed similar findings in our control patients. Thus the aetiological significance of defects in the mucinous layer is still not obvious.

The patients with interstitial cystitis demonstrated surface cells with several ultrastructural characteristics. Variations in cell size and shape were considerable and small round and larger round and polygonal cells were present. Many of the cells had impaired cell to cell contact. Round uniform microvilli and pleomorphic microvilli were often seen and all of the cell types described by Jacobs *et al.* (1981) in bladder tumours (except the IV C type) were detected in the specimens from patients with interstitial cystitis. These findings are in accordance with the results of Fukushima *et al.* (1981) on experimentally induced hyperplasia in rats and with the SEM findings in catheter-induced polypoid cystitis in humans (Anderström *et al.*, 1984a). As in our study on polypoid cystitis, pleomorphic microvilli with branching forms and bulbous tips were detected. These findings were previously reported only to appear in bladder tumours and to increase with increasing tumour grade (Jacobs *et al.*, 1976). Our results emphasise that the occurrence of pleomorphic microvilli in man is not a surface characteristic specific to urinary tract tumours. As suggested by Smith (1982), it seems more likely that their presence on the surface cells of bladder epithelium is a consequence of rapid cell turnover, resulting in migration of the intermediate cells to the surface.

In the studies of Nelson *et al.* (1979) and Jacobs *et al.* (1981), round uniform microvilli were present, but pleomorphic microvilli were not detected in specimens from patients with prostatic hyperplasia or with urinary tract infection. However, Price *et al.* (1980) observed pleomorphic microvilli in a patient with a cystoscopically and light microscopically normal bladder. In the current study, pleomorphic microvilli were detected in the control specimens although they appeared at a lower frequency than in interstitial cystitis.

One may speculate that these pleomorphic microvilli are a result of trauma to the urothelium by the instrument at cystoscopy. In an earlier study we rubbed off the superficial covering cells by the resectoscope in patients with normal bladders (Anderström *et al.*, 1984b). SEM examination of these areas revealed small round cells with long pleomorphic microvilli different from those observed in our control patients in the present study. Pleomorphic microvilli were detected in all of our control specimens, further indicating their appearance was not due to artefacts.

The SEM examination of patients with interstitial cystitis revealed disruptions in the mucinous layer, marked variability in cell size, round and pleomorphic microvilli, thick seams between cells, microridges and focally impaired cell to cell contact. These surface characteristics have earlier been described not only in bladder tumours but also in acute and chronic urinary tract infection and in polypoid cystitis. Thus changes specific to interstitial cystitis were not detected. Furthermore, the surface changes observed differed only quantitatively from those observed in the control patients and probably only reflect an increased cell turnover, which may be a result of inflammation present in the bladder.

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Development of the Invaginated Sleeve Technique for Continent Cystostomies in Dogs

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Summary—Two studies were undertaken in dogs to evaluate oblique tunnels through bladder walls lined by urothelium for use in continent cystostomies. In the first study, the tracts were lined completely by urothelium by 10 weeks, but tract calibre reduced considerably after stent removal and periluminal fibrosis was a prominent feature. In the second study a tubularised partial-thickness pedicle graft was invaginated through an oblique tunnel in the bladder wall, with the graft extending extravesically and then being wrapped in omentum. This technique provided complete urothelial covering by 2 weeks with much less periluminal fibrosis. In the 3 dogs catheterised daily up to 120 days, this technique afforded continence with generous tracts for catheterisation.

The development of improved techniques for creating continent cystostomies was advanced considerably with the evolution of the Mitrofanoff procedure in which the isolated appendix was implanted into the bladder wall to provide a continent conduit suitable for catheterisation (Mitrofanoff, 1980). The Mitrofanoff principle has since been expanded to include *any* narrow conduit with an antireflux connection to provide continence, brought to the skin from *any* urinary reservoir with intermittent catheterisation as the means of drainage (Duckett and Snyder, 1986a). As well as the appendix, tapered ileum (Eshghi *et al.*, 1986), distal ureter and a bladder tube turned back on itself to produce a competent continence mechanism (Duckett and Snyder, 1986b) have been used.

Although the Mitrofanoff principle has gained considerable popularity and is generally preferred to previously described procedures (Lapides, 1966; Schneider *et al.*, 1977; Cumming *et al.*, 1987), the techniques employed involve incorporation of non-urinary structures or considerable disruption of the urinary tract. The aim of this study was to test the hypothesis that a competent continence mechanism with an access route for intermittent catheterisation can be fashioned by forming a tract lined by urothelium in an oblique tunnel through the bladder wall.

Materials and Methods

A total of 26 adult female mongrel dogs were used; 15 were used in the first study, 9 in the second and 2 were excluded; 1 dog was sacrificed 18 days after implantation of a stent into a transmural/sub-lamina propria tunnel because of distemper and the stent could not be located in another when sought at 4 weeks.

Anaesthesia was induced with intravenous pentobarbitone (250–350 mg) and maintained with a fluorothane/nitrous oxide mixture following premedication with intravenous atropine (0.6 mg) and droperidol (1 mg/kg). An infusion of Hartmann's solution was administered intravenously per-operatively. Ampicillin (0.5 g intramuscularly) was given during the procedure and subsequently amoxycillin (0.5 g orally/day) for 7 days.

In the first group all 15 dogs underwent laparotomy via a midline incision. The bladder was bivalved in a coronal plane by diathermy. A transmural/sub-lamina propria tunnel 3 to 4 cm in length was fashioned with scissors into which a short fenestrated Silastic tube (0.5 cm outside diameter) was placed. One end of this tube extended into the bladder lumen and the other was ligated

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with 0/0 silk (Fig. 1A) and fixed to the cut bladder wall when this was closed by 4/0 Vicryl sutures.

The fenestrated tubes were left in position for predetermined periods up to 12 weeks, at which times the animals were sacrificed (dogs 1 to 7). Subsequently, 8 dogs (numbers 8–15) were sacrificed up to 4 weeks after removal of their stents at 10 weeks, including 1 dog (number 13) which was catheterised daily with an 8 F feeding tube for 11 days through a continent suprapubic cystostomy (Table 1). The catheterising tract of the dog became narrowed, and an attempt to force the catheter on day 12 resulted in a vesico-cutaneous fistula; this animal was sacrificed 2 days later on day 14.

Table 1 Group I Animals

No.	*Time to stent removal (days)*	*Subsequent time to sacrificing (days)*
1	28	0
2	42	0
3	49	0
4	56	0
5	56	0
6	84	0
7	84	0
8	70	1
9	70	3
10	70	5
11	70	7
12	70	14
13*	70	14
14	70	21
15	70	28

*Catheterised daily for 11 days, sacrificed 2 days after a traumatic vesico-cutaneous fistula developed on day 12

In the second group (10 dogs), a different procedure was evaluated. After bivalving the bladder in a coronal plane as described above, a graft of mucosa, lamina propria and some underlying muscle was raised, based on a pedicle attached just above the trigone. This graft was tubularised around a fenestrated Silastic stent (0.5 cm outside diameter) with interrupted 4/0 Vicryl sutures. A number of these sutures passed through the stent as well as the graft in order to prevent any tendency for the graft to concertina. This tubularised graft was then brought as a sleeve through a previously formed lamina propria/transmural tunnel in the bladder wall of the other half of the bivalved bladder. The bladder wall was closed with 4/0 Vicryl sutures so that the appearance was akin to a clam closing with a stent and surrounding graft protruding. This graft protrusion, wrapped by a tongue of omentum, was directed through a small gap left between the rectus abdominis muscles apposed by sutures (Figs 1B–E, 2 and 3). The bladder was fixed to the peritoneal aspect on the back of these muscles, the peritoneal cavity being closed, apart from this small window of protruding stent, graft and supporting omentum. The stent

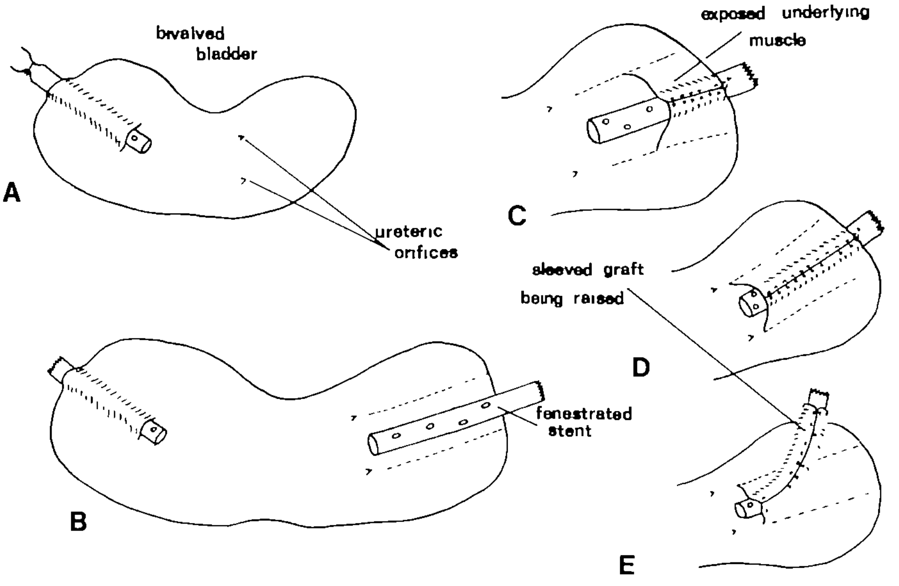

Fig. 1 (A) First study. fenestrated stent in sub-lamina propria and transmural tunnel in a bivalved bladder. (B, C, D, E) Second study. development of a tubularised pedicle graft of mucosa, lamina propria and superficial muscle around a fenestrated Silastic stent. The graft stretched readily beyond the bladder margin

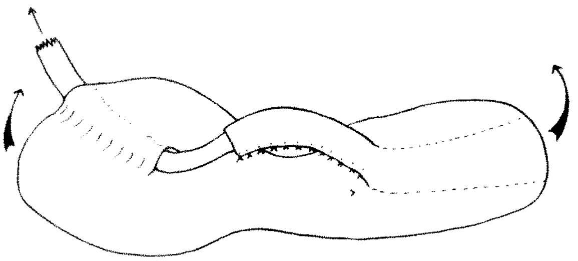

Fig. 2 Invagination of the tubularised graft through a previously formed sub-lamina propria and transmural tunnel. The graft donor site, left exposed to urine when the bladder was closed, became covered by urothelium over the next few weeks.

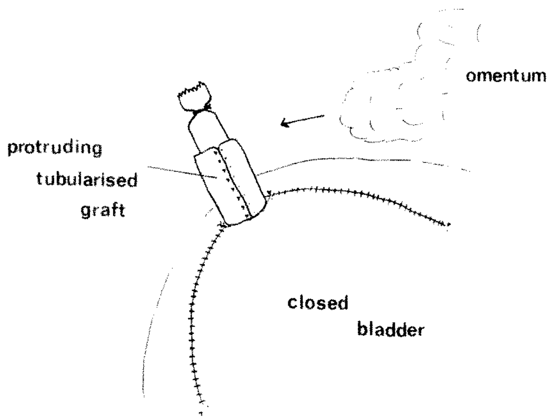

Fig. 3 Closed bladder with protruding graft surrounding Silastic stent which was then wrapped by omentum.

lumen was closed with 0/0 silk ties, then clipped before placing and fixing in a bed formed just below the skin.

Animals were sacrificed at predetermined times up to 5 weeks. In 4 dogs, stents were in position at the time of sacrificing at 2, 3, 4 and 5 weeks, and another 2 (numbers 20 and 21) had stents removed at 3 and 4 weeks and were sacrificed 3 and 4 weeks later respectively. A further 3 dogs (22, 23 and 24) were catheterised once a day (using an 8 F feeding tube) for 10 days, 14 days and 20 weeks after stent removal at 2, 3, and 3 weeks respectively. These animals were sacrificed at 2 weeks, 2 weeks and 20 weeks (Table 2).

Urine was aspirated from the bladder peroperatively at the time of stent removal and immediately before the animals were sacrificed. Specimens were examined microscopically and bacteriologically. The animals were sacrificed using intravenous pentobarbitone sodium (Lethobarb) 325 mg/ml. Macroscopic and histological examinations were made of the tunnels, catheterisation tracts and donor sites. Tissues were fixed in formalin and paraffin embedded. Sections were stained with haematoxylin and eosin haematoxylin van Gieson.

Table 2 Group II (invaginated sleeve technique)

No.	*Time to stent removal (days)*	*Subsequent time to sacrificing (days)*
16	14	0
17	21	0
18	28	0
19	35	0
20	21	21
21	28	28
22*	14	14
23†	21	14
24†	21	140

*Catheterised daily for 10 days and sacrificed 4 days later: stomal stenosis but remainder of tract healthy and patent.
†Catheterised daily for 14 and 140 days respectively.

Results

In the first procedure, partial urothelialisation of the tract was seen at 6 weeks. The tracts were within lamina propria or muscularis and were surrounded by fibrous scar tissue containing a light mixed inflammatory infiltrate of neutrophils, lymphocytes, histiocytes and plasma cells. Complete urothelialisation was present by 10 weeks, the transitional epithelial lining appearing focally attentuated but otherwise normal.

Following removal of stents at 10 weeks, a lumen of variable size persisted, being widest proximally. The tracts were partially collapsed by 5 days and at 1 or more weeks the lumina were reduced markedly in size, although transitional epithelial cell linings persisted. Abundant fibrous tissue surrounded the tracts at all stages.

In the second invaginated sleeve procedure, the tracts were present mostly within muscularis. With the stents in position at the time of sacrificing, a normal and complete urothelial lining was present by 2 weeks. A small amount of surrounding oedematous connective tissue, which contained only small numbers of mixed inflammatory cells, encircled the tracts. At 3, 4 and 5 weeks there was a slight increase in both chronic inflammatory cells and surrounding fibrous tissue. The transitional cell lining remained intact and histologically normal.

After removal of the stents at 3 and 4 weeks, then sacrificing 3 and 4 weeks later respectively (dogs 20 and 21), large lumina with complete urothelial linings persisted. These were completely surrounded by smooth muscle. There was only mild fibrosis about these tracts.

Catheterisation specimens

In the first procedure, only dog 13 was catheterised (following stent removal at 10 weeks) until day 12, when a traumatic vesico-cutaneous fistula appeared. This animal was continent until that time. The histological appearance following sacrifice at 14 days showed that although a urothelial lining persisted, the tract size had reduced markedly and contained dense periluminal fibrous tissue. Only mild inflammatory changes were observed.

In the second procedure, the 3 dogs which were catheterised (numbers 22, 23 and 24) were totally continent. Dog 22 developed stomal stenosis, limited to the urothelial-skin junction, but force was not used for fear of producing another vesicocutaneous fistula. When this animal was sacrificed and the tract probed, it was noted to be of good calibre apart from the meatal narrowing. This was confirmed histologically. All 3 tracts had healthy urothelial linings with surrounding loose connective tissue supported by muscle and omentum. There was a variable degree of mild to moderate chronic inflammation throughout the tracts (Fig. 4).

Donor sites

Macroscopically, the graft donor sites were indistinguishable from the rest of the bladders. There appeared to be no reduction in bladder wall area based on the position of marker clips applied at the time of graft formation and tubularisation. By 2 weeks, the donor site was partially covered by transitional epithelium showing regenerative atypia with underlying granulation tissue and immature oedematous scar tissue. There were moderate numbers of mixed inflammatory cells at this time. Subsequently, a normal mucosa and a lamina propria showing small amounts of scar tissue were present at these sites.

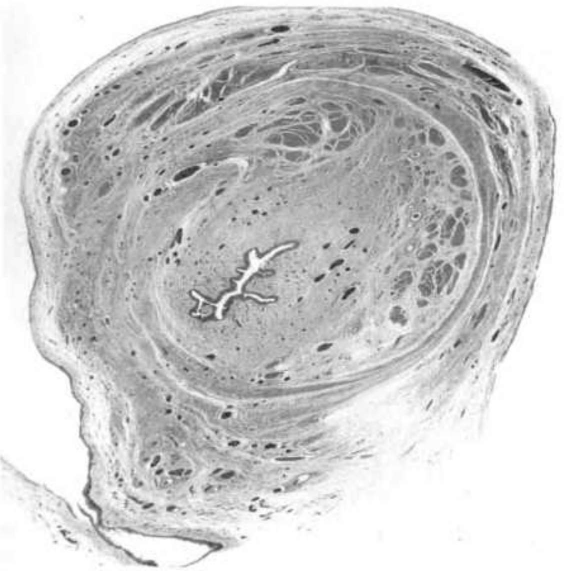

Fig. 4 Transverse section through bladder wall showing a generous lumen lined by urothelium with surrounding muscle (H and E ×8.5).

Bacteriuria

In the first group, bacteria were detected in only 2 instances from bladder aspirates. At 21 weeks, dog 6 had calcareous deposits on the stent which had eroded through part of the tunnel, *Staphylococcus aureus* having been cultured ($>10^5$ organisms/ml) from the suprapubic aspirate. Dog 15 had *Staphylococcus epidermis* (6×10^4 organisms/ml) cultured from the urine collected when the stent was removed, but the subsequent urine obtained at the time of sacrificing was sterile.

In the second group, dogs 16 and 21 had bacteria cultured from urine. In the former a light mixed growth of gram negative organisms was seen from urine obtained immediately prior to sacrificing; in the latter, *Pasteurella* species ($>10^5$ organisms/ml) was cultured, but the urine specimen obtained immediately prior to sacrificing this animal 4 weeks later was sterile. Bladder urine from the 4 dogs catheterised daily through their continent cystostomies was sterile, except for dog 24 from week 19, when *Staphylococcus aureus* was cultured consistently, although the dog was constitutionally normal and urinary leukocytosis was absent.

Discussion

The main problem for urologists in their efforts to fashion continent urinary reservoirs has been the creation of a stable, continent valve (Handley Ashken, 1987). Both techniques examined in this study resulted in competent continence mechanisms, but the invaginated sleeve technique also afforded a generous conduit diameter to facilitate passage of a catheter, which the former procedures failed to provide.

Histologically, normal transitional epithelial cells lined the tunnels, although the invaginated sleeve technique was markedly superior in terms of time to complete urothelial covering, resulting luminal size and a considerably lesser tendency to periluminal fibrosis. Extravasation of urine occurring via the fenestrated stents, together with trauma related to bladder filling and emptying about these stents, may have contributed to this tendency to fibrosis, particularly with the former group. Whether continuous catheter drainage of the bladder would have lessened this tendency to scarring is conjectural, since it was not a practical proposition in these studies.

In the second procedure, the tubularised pedicle graft stretched readily, so that graft easily extended several cm beyond the bladder wall after invagination through the sub-lamina propia/transmural tunnel and closure of the bivalved bladder. Viability of this urothelial extension was assured by a generous wrapping of omentum, the merits of which have been reported previously (Gardiner *et al.*, 1984). In the second group, the only "tract failure" was a discrete meatal stenosis; the remainder of the catheterising route was patent with a healthy urothelial lining. When the stomas were formed immediately after stent removal at 2 and 3 weeks, identification of urothelium as opposed to granulation tissue was difficult, so these results indicate excellent vascularity of those parts of the grafts protruding beyond the bladder from both the pedicle itself and supporting omentum.

Infection was not a problem in these experiments. Two dogs (numbers 6 and 16) had *Staphylococcus* and a light mixed growth of coliform organisms respectively cultured from bladder aspirates obtained immediately prior to sacrificing. Stents were *in situ* in both cases and a urinary leukocytosis was present. The staphylococcal and *Pasteurella* organisms cultured from bladder aspirates from dogs 15 and 21 respectively at the times of stent removal were probably surgical contaminants, since the animals were clinically normal and urine specimens contained normal numbers of leukocytes. Similarly obtained samples 28 days later at the time of sacrificing were sterile. Bladder urine specimens from the 4 dogs catheterised daily through their continent suprapubic cystostomies were sterile to culture with the exception of dog 24, from which *Staphylococcus aureus* was grown from week 19. This was most probably a skin contaminant introduced with catheterisation, since the dog remained well and urinary leukocyte numbers were normal.

The results of the procedure examined in the second study were superior to those from the initial approach. In addition, with this invaginated sleeve technique there does not appear to be any reduction in bladder capacity, the denuded graft donor site being covered rapidly by urothelium with supporting connective tissue stroma. This technique is simple and does not involve the use of extra-urinary tract structures, with the exception of omentum, providing an effective method for continent suprapubic urinary diversion. Consideration of its use in carefully selected patients may provide an additional treatment option for those with refractory continence problems.

Acknowledgements

We are indebted to the Departments of Medical Illustration at the University of Queensland and Royal Brisbane Hospital and, in particular, to those members of the Department of surgery involved in the care of the animals used in these studies.

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Bonney's Blue Cystitis: a Warning

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Summary—The instillation of diluted Bonney's blue into the bladder during gynaecological operations has been quite common practice over the last 50 years. Bonney's blue is composed of a 1:1 mixture of brilliant green and crystal violet dissolved in ethanol (90%) or industrial methylated spirit. Before insertion into the bladder this solution must be diluted with water to a 0.5% solution. Failure to do this will result in a severe inflammatory reaction within the bladder. The degree of resultant damage depends upon the duration of exposure. Persistent pain is a feature of this condition, although the other symptoms (frequency and urgency) may settle in time. Two cases of chemical cystitis resulting from the use of undiluted Bonney's blue are described to illustrate the possible consequences. Both patients were awarded 6-figure sums as compensation.

Victor Bonney (gynaecological surgeon to the Middlesex Hospital from 1908 to 1937) originally developed his solution for the preparation of the vagina or skin during gynaecological operative procedures (Bonney and Browning, 1918). Bonney's blue diluted with water has also been used to determine the patency of the fallopian tubes and to demonstrate vesicovaginal fistulae.

Bonney's blue consists of a 1:1 mixture of brilliant green (4-{4-diethylaminobenzhydrylidene} cyclohexa 2,5-dien-l-ylidenediethylammonium hydrogen sulphate) and crystal violet [4,4′ Bis (dimethylamino) benzhydrilene] cyclo-hexa-2,5-dien-l-ylidenedimethyl ammonium chloride diluted in alcohol (90%) or industrial methylated spirit. These constituents are potentially toxic to mucosal membranes and for this reason the solution should be diluted with water to a 0.5% concentration before instillation into the bladder or contact with any other mucosal surface. This solution and methylene blue are both freely available in most operating theatres and confusion between the two is therefore likely to occur. Adequate dilution of either solution has not been reported to cause tissue damage in routine clinical practice.

Patients and Methods

Two patients referred to the Middlesex Hospital with a view to reconstructive surgery, and to the Medical Protection Society for medico-legal reasons, had suffered chronic chemical cystitis as a result of intravesical instillation of undiluted Bonney's blue.

Case Reports

Case 1 A 32-year-old woman with a history of menorrhagia underwent total abdominal hysterectomy and postoperatively was found to have developed a pelvic haematoma, which was treated conservatively. She gave no history of previous urinary symptoms. She had a persistent vaginal discharge for 2 months and this was thought to be due to a vesicovaginal fistula. A "Bonney's blue test" was ordered by the consultant and performed on the ward by a junior doctor unfamiliar with the procedure. Unfortunately 20 ml of undiluted Bonney's blue were inserted into the bladder via a catheter for 20 min, resulting in severe acute chemical cystitis. No vesicovaginal leak was demonstrated. Suprapubic pain, dyspareunia, urgency and marked frequency of micturition lasted for nearly 2 years. During this period 3 cystodistensions performed under general anaesthesia were of little symptomatic benefit. An augmentation ileocystoplasty was performed, but suprapubic pain, recurrent urinary tract infections, frequency and urge

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incontinence persisted. On referral to our unit a videocystometrogram demonstrated mild detrusor instability, a capacity of 700 ml, no stress incontinence and a small ileocystoplasty A supratrigonal denervation, vaginal obturator shelf repositioning and removal of ileocystoplasty were performed Following this the recurrent urinary tract infections were improved but the patient was left with intractable suprapubic discomfort, frequency, urge incontinence and enuresis, and a functional bladder capacity of approximately 250 ml.

Case 2 A 39-year-old woman underwent a total abdominal hysterectomy and colposuspension for menorrhagia and stress incontinence. Per-operatively, undiluted Bonney's blue instead of methylene blue was instilled by mistake and left within the bladder for nearly 2 h. Severe suprapubic pain, urgency and frequency occurred in the immediate post-operative period. Irrigation with 3 l of sterile water and then 3 l of glycine was performed though a suprapubic catheter and the patient was then transferred to our unit. A cystoscopy performed 3 weeks later revealed generalised mucosal inflammation and a bladder capacity of only 50 ml. The suprapubic catheter was removed but pain, frequency and recurrent urinary infections persisted. A further cystoscopy 4 weeks later showed severe inflammation and ulceration but an increased capacity of 250 ml. Systemic steroids (prednisolone 30 mg/day) and long-term, low-dose antibiotics were commenced. Over the following year the steroids were reduced and after 4 cystodistensions under general anaesthesia an increase in capacity to 600 ml resulted. However, suprapubic pain persisted and treatment with dimethyl sulphoxide bladder instillation failed to improve this.

The pain persists 2 years after the chemical injury, but relief has been achieved using a transcutaneous nerve stimulator and the bladder capacity is 700 ml.

Discussion

A single case of haemorrhagic cystitis following the accidental insertion of a small amount of gentian violet (1% crystal violet in 2% alcohol) into the urethra during self-vaginal lavage has been described (Walsh and Walsh, 1986). As in the present 2 cases, severe pain, urgency, frequency and haematuria resulted.

Cystitis following intravesical instillation of alcohol alone has not been described. However, other organic solvents are known to induce an inflammatory reaction after contact with bladder urothelium. The experimental instillation of 10% formaldehyde into rabbit bladders for 15 to 90 min resulted in varying degrees of cystitis according to the duration of exposure and the extent of the subsequent saline lavage. The damage produced ranged from superficial cystitis to transmural necrotising cystitis at either end of the spectrum (Kumar, 1979). The use of ether to dissolve Foley catheter balloons is now discouraged following reports of chemical cystitis after its insertion (Rosencrantz and Carr, 1971; Nellans *et al.*, 1985).

Chemical damage to the bladder epithelium other than by organic solvents has also been described. The accidental intravesical insertion of an acidic spermicidal contraceptive suppository has been shown to cause chemical cystitis.

Crystal violet, in its pure undissolved form, has been shown to interact with cellular DNA and hence should be regarded as a potential mutagen (Rosencrantz and Carr, 1971). It may also induce severe necrotic skin reactions and necrosis of oral mucosa after local application (John, 1968).

It seems, therefore, that both alcohol and crystal violet, as constituents of Bonney's blue, are independently capable of causing an inflammatory reaction when exposed to bladder urothelium. For this reason Bonney's blue in its undiluted alcohol-based form should be regarded as potentially toxic. Because of this and the fact that absorption of crystal violet may occur across mucous membranes, Bonney's blue and gentian violet should be reserved for preparation of the vagina and skin (*Pharmaceutical Journal*, 1987).

The cases reported here were characterised by an initial acute intravesical inflammatory reaction, followed by a more chronic clinical course characterised by reduced bladder capacity and associated features suggestive of a sensory bladder disorder. The pathogenesis of these changes is unknown but it seems likely that they were consequent upon the initial chemical damage. Both mechanical and neural factors contributed to the clinical picture.

Toxic damage to the structural constituents of the bladder wall will result in intramural fibrosis and the subsequent reduction in bladder compliance will result in a reduced functional bladder capacity.

It seems likely that neural damage will be a prominent feature of this picture and subsequent loss of cholinergic motor fibres will potentially result in denervation of the muscle and associated denervation hypersensitivity. This process is well recognised in association with prostatic outflow obstruction, where it is implicated in the pathogenesis of the accompanying detrusor instability (Sibley, 1984; Gosling *et al.*, 1986).

Although the afferent innervation of the bladder is poorly understood, it is recognised that there is a dense submucosal neural plexus comprising acetylcholinesterase-positive and putative neuropeptidecontaining neurones which are likely to be important in the perception of bladder sensation (Elbadawi and Schenk, 1966; Gu *et al.*, 1984; Maggi and Meli, 1986). This submucosal network is closely related anatomically to the lining urothelium and is therefore potentially very susceptible to toxic damage by intravesical chemicals. Initial sensory nerve stimulation, either directly by the noxious substance or subsequently by the release of endogenous kinins and related mediators of inflammation, will produce marked discomfort. Subsequent neural damage and regeneration could lead to altered bladder sensation with associated alteration of the functional bladder capacity and voiding pattern. From this it is apparent that there is a wide spectrum of pathological processes at work which result in the severe disruption of bladder function exemplified by the cases reported here.

It is important not to carry out definitive treatment of these patients at too early a stage in their natural history before the full pathological process has expressed itself.

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The Effects of Cromakalim on the Detrusor Muscle of Human and Pig Urinary Bladder

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Summary—The effects of cromakalim, a potassium channel activating drug, have been studied on isolated detrusor muscle strips from normal Landrace boar, normal and unstable mini-pig and unstable human bladder. Cromakalim abolished spontaneous activity in all strips but did not abolish the ability of the detrusor muscle from any of the specimens studied to respond to carbachol, increased extracellular K^+ or transmural nerve stimulation.

Intravenous infusion of cromakalim in the urethral obstructed mini-pig caused the characteristic unstable contractions associated with bladder outflow obstruction to be abolished, leaving the animal able to void.

Experiments with potassium isotopes and the sucrose gap technique demonstrated that cromakalim increased the potassium permeability and hyperpolarised the cell membrane, consistent with its reported actions on other smooth muscles.

These results suggest that drugs such as cromakalim, which act by reducing membrane excitability without inhibiting responses to existing innervation, may have a clinical application in the treatment of instability which is secondary to bladder outflow obstruction.

Detrusor muscle instability is a major cause of urinary incontinence (Torrens and Hald, 1979) but its treatment remains unsatisfactory. This is largely due to a lack of understanding to the underlying pathophysiology of the condition. Models of detrusor instability secondary to bladder outflow obstruction, both in Landrace pig (Sibley, 1985) and Göttingen mini-pig (Speakman *et al.*, 1987) have been developed in our laboratory. Anatomical and physiological studies based on these models show that instability in the pig is associated with smooth muscle denervation and supersensitivity (Sibley, 1987; Speakman *et al.*, 1987). Recent evidence on the innervation (Gosling *et al.*, 1986) and physiology (Harrison *et al.*, 1987) of human detrusor smooth muscle taken from patients with bladder instability secondary to bladder outflow obstruction suggests that a similar association may be found in man. If this is the case, the traditional treatment aimed at reducing the effects of the excitatory innervation of the detrusor may be inappropriate and it might be more profitable to direct attention towards drugs which directly inhibit the excitability of the smooth muscle itself.

Cromakalim is one such drug. It has been investigated as an antihypertensive agent, since it causes relaxation of isolated blood vessels (Hamilton *et al.*, 1986; Weir and Weston, 1986a). It also relaxes longitudinal gut muscle (Weir and Weston, 1986b) and trachealis (Allen *et al.*, 1986). The effects appear to be due to activation of K^+ channels in the smooth muscle membrane, resulting in hyperpolarisation. This novel effect is shared by other drugs, such as nicorandil (Furukawa *et al.*, 1981) and pinacidil (Weston and Abbott, 1987). This report details the effects of cromakalim on normal and unstable detrusor smooth muscle of the pig *in vitro* and *in vivo*, and on unstable human detrusor *in vitro*.

Materials and Methods

Bladder outflow obstruction was produced in recently weaned Landrace pigs and Göttingen mini-pigs (male and female) by placing silver rings around the proximal urethra under halothane

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anaesthesia (Speakman *et al.*, 1987). In order to study the anatomical and physiological changes in the development of instability, biopsies of the detrusor muscle were obtained from animals shown by urodynamic assessment to have detrusor instability 3 to 12 months after the obstruction. Detrusor from normal animals was obtained from control mini-pigs, and from the abattoir for the Landrace pigs.

Urodynamic assessment was performed in conscious animals, using either standard urodynamic cannulae or a radiotelemetry system with a radiotransmitter pill placed in the bladder at laparotomy. The bladder was filled either with a filling catheter at a rate of 10 to 15 ml/min or by forced diuresis with intravenous saline and frusemide (0.5–2 mg/kg). The urodynamic catheters were connected to Bell and Howell type 4-422 physiological pressure transducers and the radiotelemetry signals were transmitted to a Type 7040 receiver (Remote Control Services, London). The responses were recorded on a Servoscribe 2S two channel pen recorder. Biopsies from the anterior wall of the detrusor of human bladder were obtained at surgery from patients shown by urodynamic assessment to have bladder instability secondary to outflow obstruction. In both pigs and humans, bladders showing transient repeated increases in intravesical pressure of more than 15 cm H_2O during filling were considered to be unstable.

Smooth muscle strips comprising parallel muscle bundles were dissected from the detrusor muscle under a binocular microscope. For tension recording, strips measuring 1 × 1 × 7 mm were mounted in a superfusion apparatus (Brading and Sibley, 1983) in which 6 strips could be studied simultaneously. Each strip was suspended by cotton threads in a 0.2 ml organ bath with recessed platinum ring electrodes 1 cm apart in the walls, and superfused with warmed (35–37°C) Krebs solution at a flow rate of about 1 ml/min. The composition of the Krebs solution was (mM): NaCl 120; KCl 5.9; $NaHCO_3$ 15.4; $MgCl_2$ 1.2; NaH_2PO_4 1; $CaCl_2$ 2.5; glucose 11. All solutions were equilibrated with 97% O_2, 3% CO_2, warmed to 35 to 37°C. Tension was measured isometrically using home-mounted Akers transducers or Pioden UF1 transducers and recorded on a multichannel pen recorder (Watanabe). A resting tension of 1 g was applied initially to each strip and at least 1 h allowed for equilibration. Contractile responses were expressed as a percentage of a control response to a 10-s application of 10^{-4}M carbachol applied at the beginning of the experiment Activation of intrinsic nerves was achieved by electrical field stimulation (50 V, 0.05 ms, 5-s train, variable frequency).

Slightly larger strips were used for flux studies. ^{43}K efflux was followed from strips mounted and slightly stretched on stainless steel holders using fine silver wire, and loaded for at least 3 h in Krebs solution containing 1.5 to 3 μC/ml ^{43}K. Radioactivity was washed out of the tissues in a superfusion apparatus at a flow rate of 1 ml/min. The superfusate was collected in 2-min samples which were counted in a gamma scintillation counter. The last sample contained the tissue. Tissue counts at each time were calculated by summing in reverse order. The instantaneous rate of efflux was calculated by dividing the counts leaving the tissue during a 2-min interval by the mean counts in the tissue during that interval; the 10-min uptake of ^{43}K was measured by exposing the tissues to tracer in the appropriate Krebs solution and then washing for 5 min in ice-cold tracer-free Krebs to remove extracellular tracer before counting the tissues.

The effects of cromakalim on the electrical properties of the tissues were measured using a double-sucrose gap apparatus, with rubber diaphragms separating the solutions as described by Ito *et al.* (1977). This apparatus allows extracellular recording of changes in membrane potential of cells bathed in Krebs solution in a central node 0.5 mm wide. The potential difference between the central node and tissue depolarised in high K^+ solution is measured across a sucrose gap of 2 mm, in which the tissue is surrounded with isotonic sucrose solution, ensuring that the majority of current flows through the cells and not in the extracellular space. Current pulses are injected across a second sucrose gap, allowing depolarisation and hyperpolarisation of the cells in the central node. Tension can be recorded simultaneously.

Cromakalim was a gift from Beechams Pharmaceuticals. It was made up as a stock solution of 10^{-2}M with 70% ethanol and diluted when appropriate with Krebs solution. Carbachol was supplied by Sigma and was made up as a stock solution of 10^{-2}M in distilled water and subsequently diluted with Krebs. High potassium solutions were made by increasing the KCl content of the Krebs at the expense of NaCl. The results are expressed as mean ±SE (n) and statistical significance was assessed using a paired *t* test. Values of *P* are indicated as follows: less than 0 1 (*), 0.05 (**) and 0.01 (***).

Results

The effects of cromakalim on contractile activity

(a) *Spontaneous activity* in vitro. The majority of detrusor strips from normal (60% human, n = 36; 67% pigs, n = 120) and unstable (70% human, n = 78; 79% pigs, n = 180) bladders showed spontaneous mechanical activity during the course of an experiment and the percentage was higher if the strips were left undisturbed in normal Krebs solution. Cromakalim inhibited spontaneous activity in all of the species examined and reduced baseline tension when this was present. This inhibition of spontaneous activity usually occurred within 1 min of adding the drug. The time taken for reappearance of activity after washout of the drug was concentration-dependent. In the obstructed mini-pig, 6 of 8 strips showed a reduction in the frequency of spontaneous activity at a concentration of 10^{-7}M and complete cessation was seen in all strips at concentrations above 5.10^{-7}M. In control mini-pig bladder the myogenic activity was inhibited in 3 of 7 strips at a concentration of 10^{-7}M; again, complete cessation of spontaneous activity occurred in all strips at 5.10^{-7}M. Figure 1 illustrates the effects of several concentrations of the drug on detrusor from a control mini-pig. In normal tissues the spontaneous contractions almost always relax to the baseline, so that there is little basic tone and cromakalim just affects the frequency. Strips from unstable bladders occasionally have spontaneous activity in which a degree of fusion of the contractions occurs, and in these strips cromakalim reduced basic tone.

Figure 2 shows examples of this effect on unstable detrusor from mini-pig and human bladders; note the potentiated spontaneous contractile activity after washout of cromakalim. However, it was impossible to find a condition in which the detrusor smooth muscle remained tonically contracted for long enough to construct an accurate dose-response curve for the relaxant effect of cromakalim.

(b) *Contractile responses to agonists and transmural nerve stimulation* in vitro. Figures 3 and 4 show the dose-response curves for the contractile responses of detrusor from normal and unstable mini-pig, unstable human and normal Landrace pig bladders to carbachol and potassium. Carbachol was applied for 10 s and increased K$^+$ concentrations for 4 min. Responses are expressed as a percentage of that achieved in 10^{-4}M carbachol. The effect of cromakalim (10^{-5}M) on these responses is also shown on each graph. Cromakalim shifts the dose-response curves to carbachol to the right in normal and unstable mini-pig bladders and there is a slight but significant decrease in the maximum response in the normal bladder. In unstable human bladders the response to carbachol is reduced at all concentrations, and in the normal Landrace pig the responses to low concentrations are inhibited, but the response to 10^{-4}M is only slightly decreased. The responses to increased K$^+$ concentrations are somewhat reduced in the presence of cromakalim in all tissues at all K$^+$ concentrations. It should be noted, however, that the effects of cromakalim were

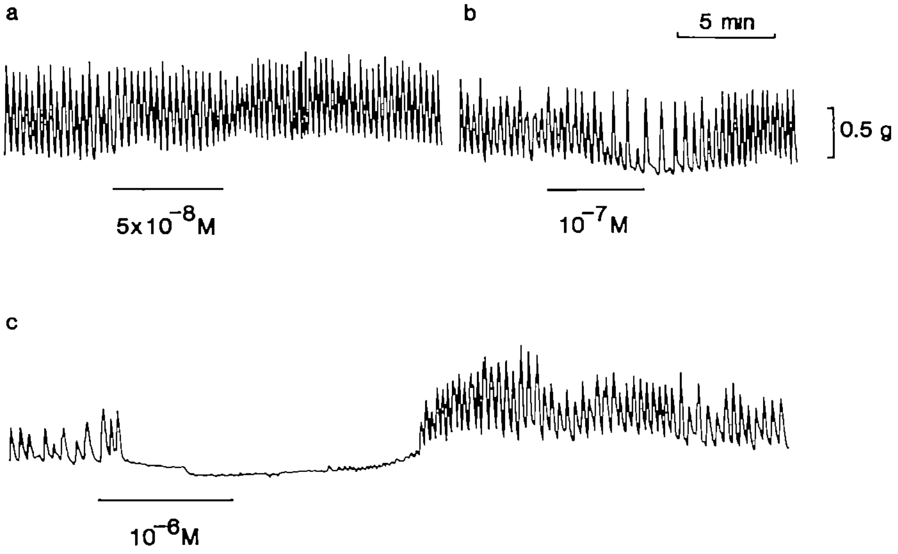

Fig. 1 The effect of cromakalim on spontaneous activity from detrusor muscle of a normal mini-pig. No effect is seen at 5.10^{-8}M cromakalim, while 10^{-7}M clearly reduces the frequency of the spontaneous activity. 5.10^{-7}M cromakalim totally inhibits the spontaneous contractions. There is little maintained tone in this strip.

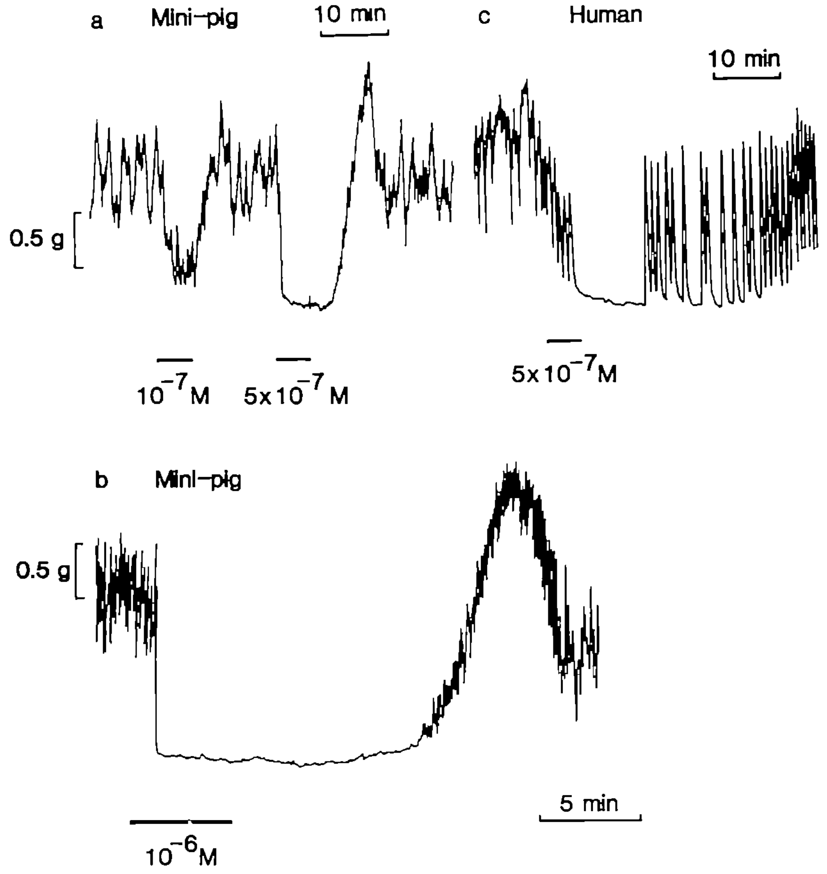

Fig. 2 Examples of the effect of cromakalim on unstable detrusor from mini-pig and human bladders

examined after the control responses had been obtained in the same tissues, and we have some evidence (unpublished) that tissue responsiveness may decline with time.

Figure 5 shows the effect of transmural nerve stimulation in all of the species studied. The frequency response curves are not significantly affected by cromakalim.

(c) *Bladder contraction* in vivo. Figure 6 shows the filling and voiding urodynamics of an obstructed mini-pig. During filling, regular unstable contractions of 15 to 20 cm H_2O were seen. Cromakalim (0.3 mg/kg) completely abolished these contractions but the pig voided normally. The effect of cromakalim lasted 40 min and was reversible. Cromakalim (dose range 0.1–0.3 mg/kg) abolished the unstable contractions in all of the pigs investigated (3) but caused a substantial drop in mean arterial blood pressure in all animals studied (mean decrease = 30 mmHg for 0.3 mg/kg).

Investigation of the mechanism of action of cromakalim

(a) *Effect on electrical properties of the cell membranes.* Figure 7 shows the results obtained from detrusor smooth muscle of an unstable pig using the double sucrose gap. The upper trace shows the membrane potential and the lower shows the contractile response of the cells in the node. Depolarising and hyperpolarising current pulses were applied alternately. Each depolarisation elicited a spike-like membrane response (reflecting the summed activity of the cells in the node) which triggered a phasic contraction. The application of cromakalim 10^{-5}M reduced the size of the phasic contractile responses, caused a progressive hyperpolarisation of the membrane and a reduction in the membrane resistance (seen by the reduced voltage response to injection of a fixed current). This suggests that the drug is causing a progressive increase in K^+ conductance of the membrane, leading to a hyper-

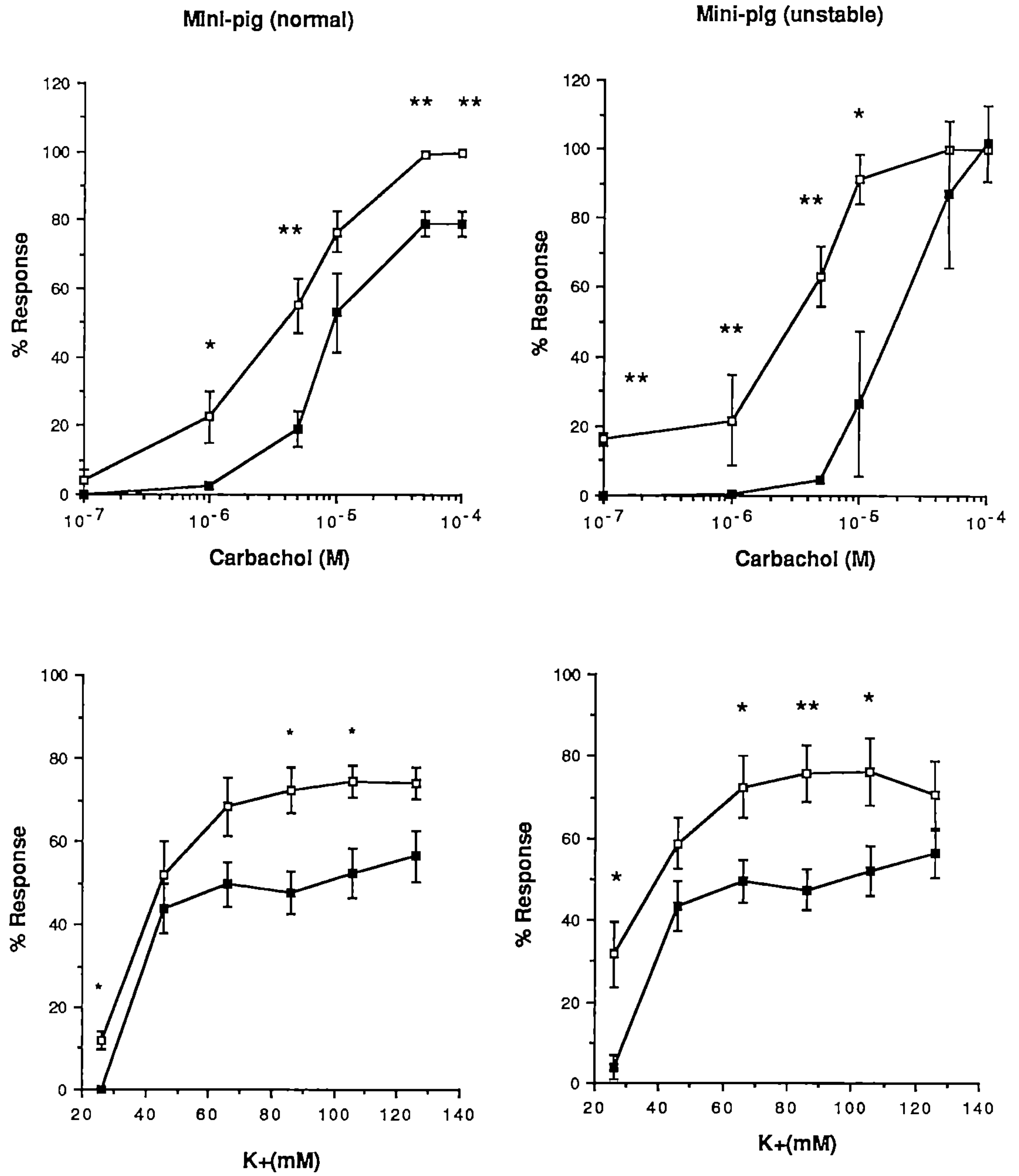

Fig. 3 Dose-response curves of the contractile responses of strips of unstable (n=10) and normal (n=8) mini-pig detrusor to carbachol (10 s) and potassium (4 min) in the presence (■) and absence (□) of cromakalim (10^{-5}M) Contractions expressed as a percentage of the response obtained to 10^{-4}M carbachol.

polarisation and a reduction in the number of cells brought to threshold for action potential production by the depolarising current, and hence a reduced contractile response. Note that after a certain degree of hyperpolarisation the contractile activity in response to depolarisation is abolished and the tissue relaxes. Satisfactory records of the membrane properties of normal pig bladder with the double sucrose gap could not be obtained. This seems to be due to the fact that the cells are less well coupled in the normal bladder and sufficient current cannot flow from cell to cell in the node to allow this

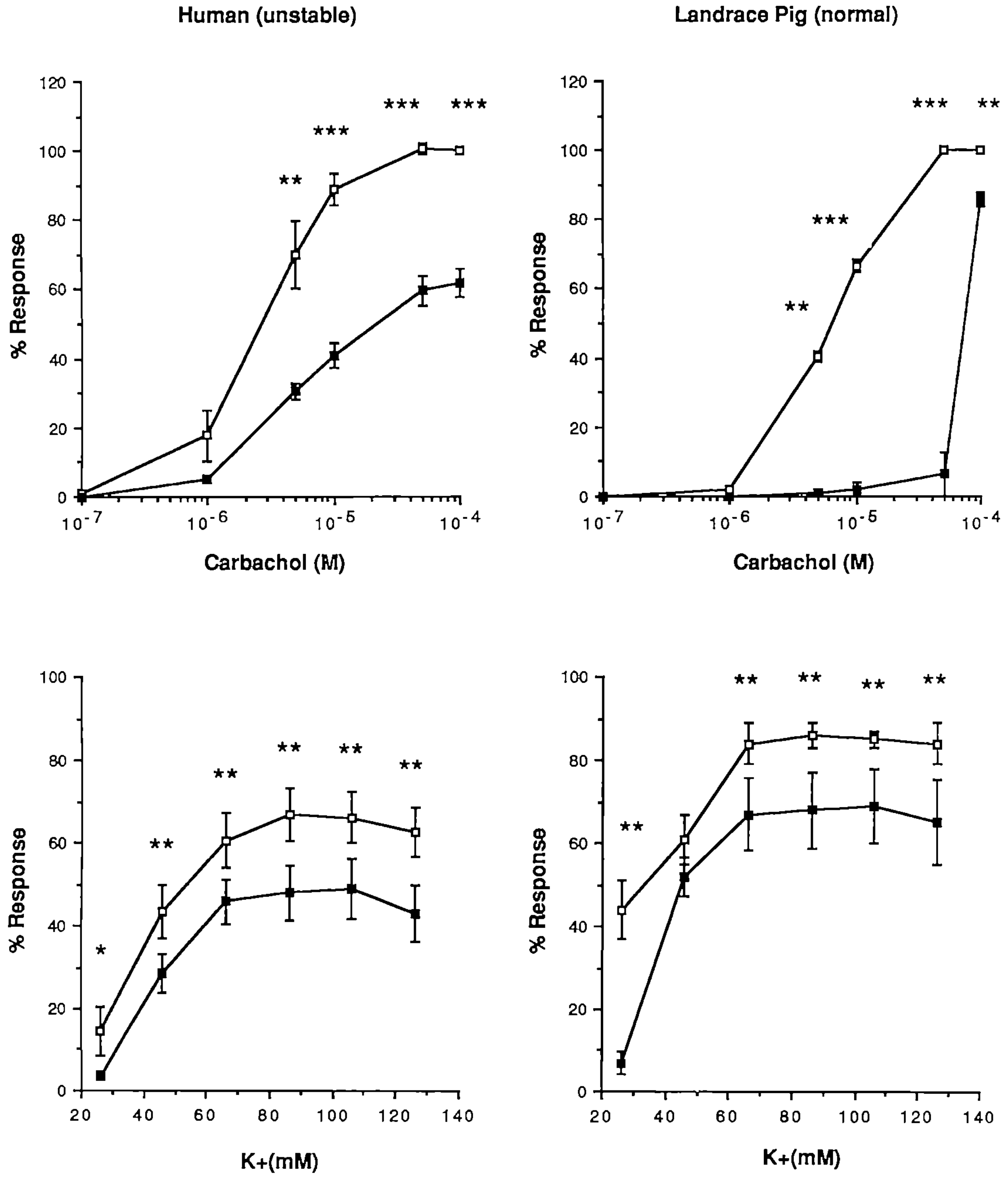

Fig. 4 Dose-response curves of the contractile responses of unstable human (n=6) and normal Landrace pig detrusor (n=12) to carbachol (10 s) and potassium (4 min) in the presence (■) and absence (□) of cromakalim 10^{-5}M. Contractions expressed as a percentage of the response obtained to 10^{-4}M carbachol.

method of recording to be used. This interpretation is backed up by preliminary measurements of the length constants of muscle bundles from normal and unstable pig bladders using the method of Abe and Tomita (1968).

(b) *Effect on ^{43}K fluxes.* Figure 8 shows the effects of cromakalim on the rate of loss of ^{43}K from the detrusor of normal and unstable bladders from mini-pigs. Full efflux curves are shown for the effects of 5.10^{-6} and 5.10^{-5}M cromakalim and the

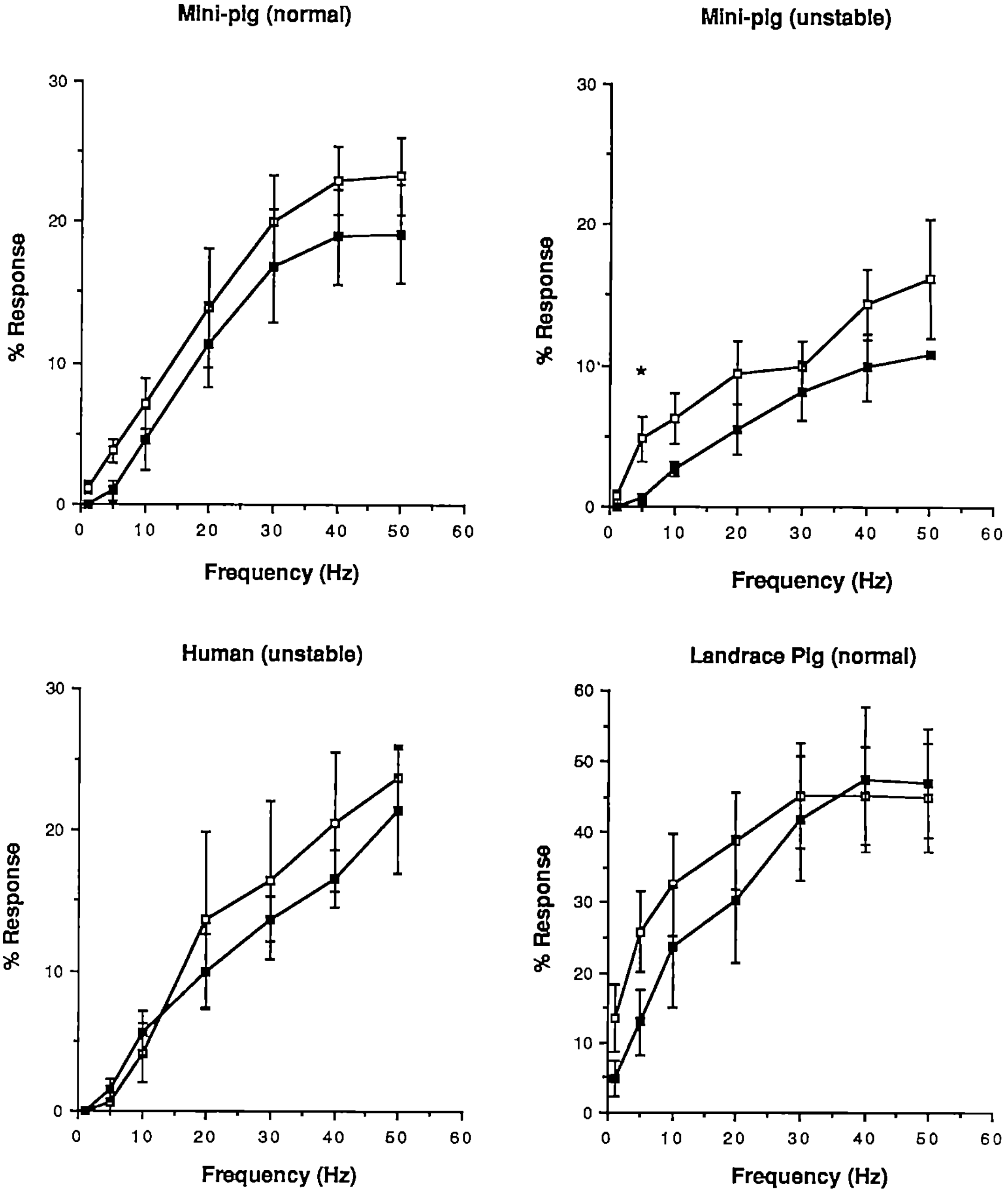

Fig. 5 Response to intramural nerve stimulation in normal Landrace boar (n = 12), unstable human (n = 6), normal (n = 8) and unstable (n = 10) mini-pig bladders Field stimulation at 50 V, stimulus duration 0.05 ms, 5-s train of impulses, in the presence (■) and absence (□) of cromakalim 10^{-5}M. Contractions expressed as a percentage of the response obtained to 10^{-4}M carbachol

histograms show the mean percentage increase in efflux rate achieved during the course of the drug application, as a function of concentration. The rate is increased by cromakalim dose-dependently and the unstable detrusor is more sensitive to the drug than the normal detrusor, in which an increase in efflux rate is not seen at concentrations lower than 10^{-5}M, although these have a clear effect on the spontaneous activity. The uptake of ^{43}K is also increased by cromakalim (10^{-5}M), as shown for

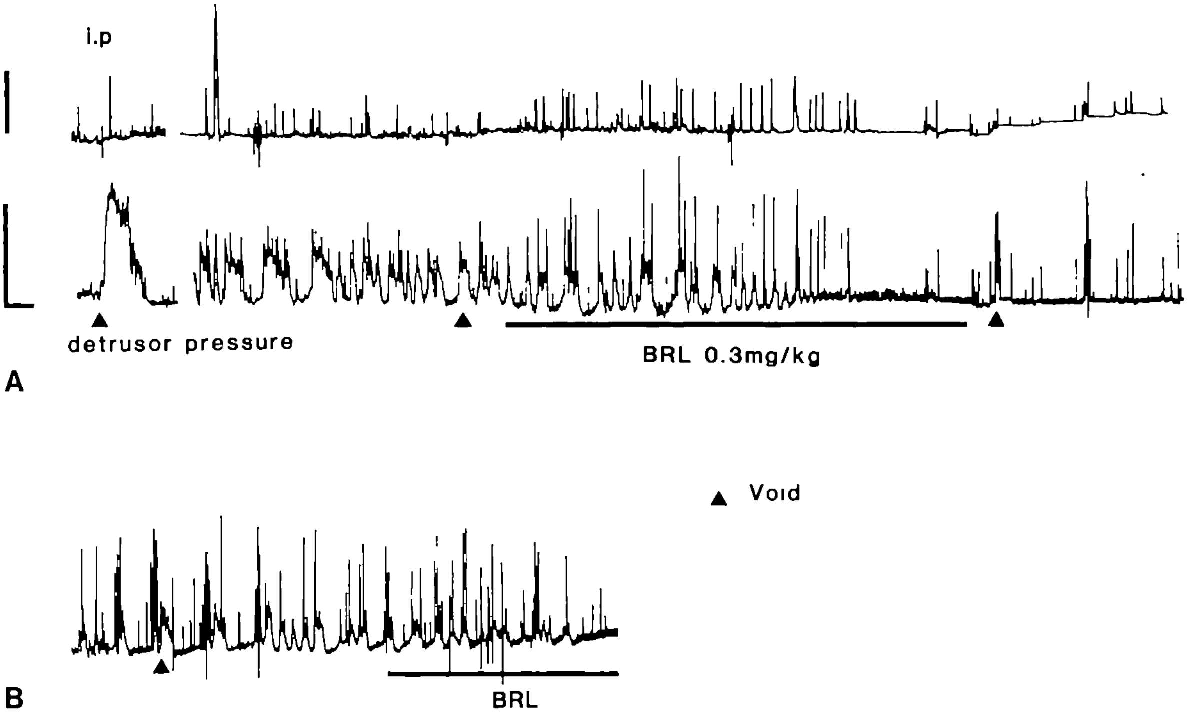

Fig. 6 Urodynamic study showing unstable contractions in a mini-pig 3 months after obstruction (A) The top trace is intraperitoneal pressure and the bottom trace detrusor pressure The bladder was filled by a forced diuresis with intravenous boluses of frusemide (1 5 mg/kg) Cromakalim (0.3 mg/kg) was applied for the time period shown Closed triangles indicate bladder voiding. (B) Continuation of detrusor pressure from (A) showing reapplication of cromakalim Vertical lines represent a pressure of 30 cmH_2O and horizontal lines are equivalent to a time period of 2 min

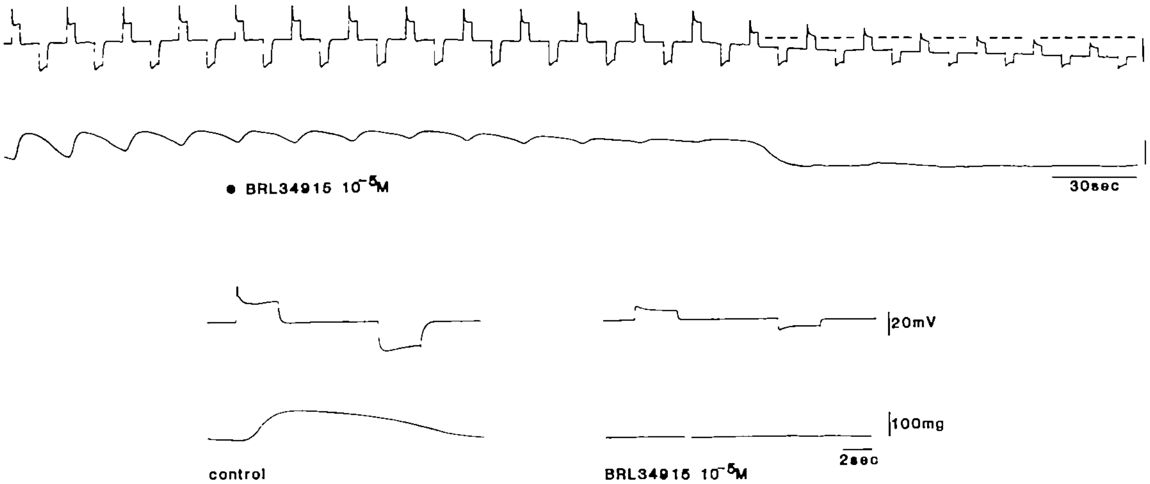

Fig. 7 Double sucrose gap record showing the effect of cromakalim on unstable mini-pig detrusor The upper of each pair of traces records membrane potential and the lower tension. Alternate depolarising and hyperpolarising current pulses were applied, depolarisation eliciting spikes and phasic contractions in normal solution Cromakalim (10^{-5}M) hyperpolarised the membrane, reduced the size of the electrotonic potential and relaxed the tissue. Lower traces show responses before and after the application of cromakalim with an expanded time scale

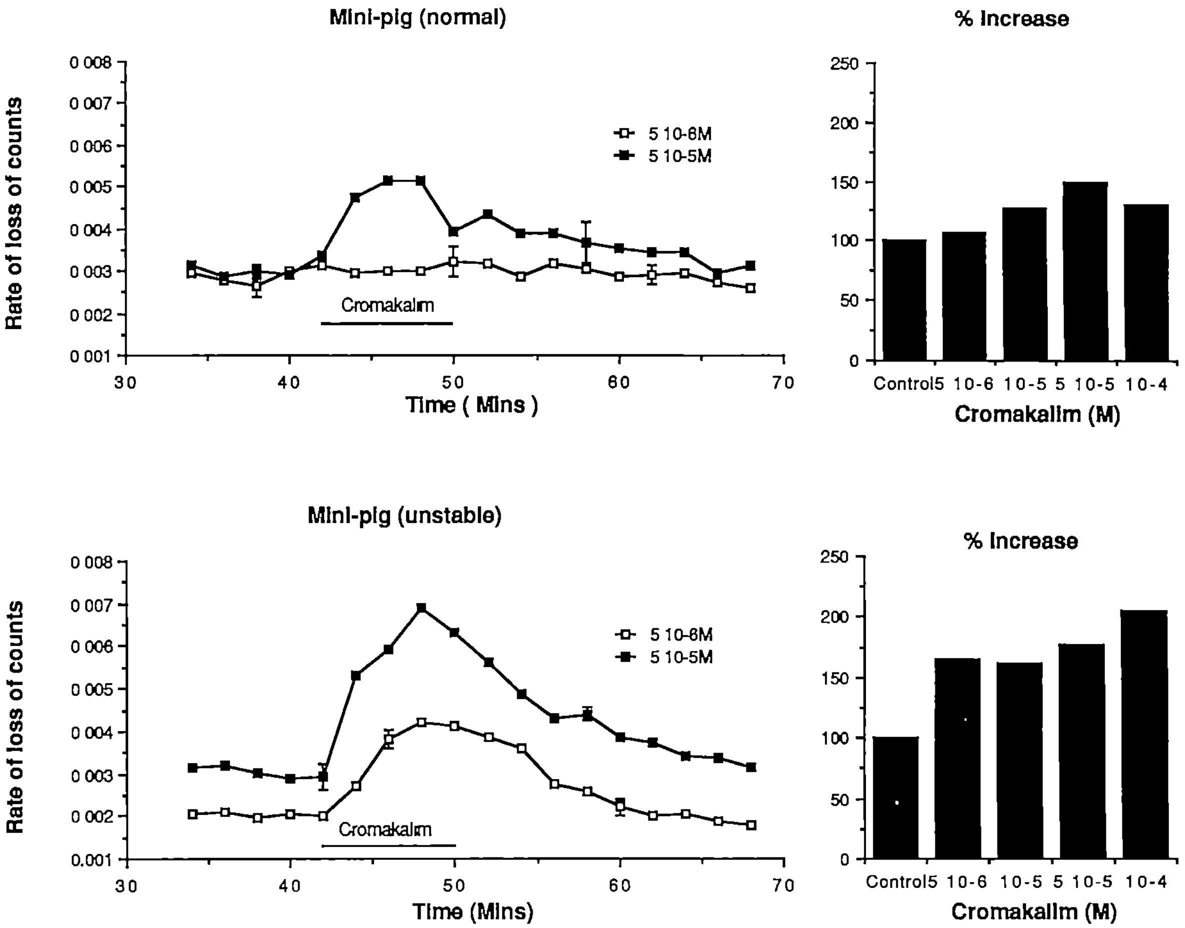

Fig. 8 The cromakalim stimulated efflux of ^{43}K from strips of stable and unstable mini-pig detrusor muscle (n = 3 for each concentration shown) Full efflux curves are given showing the effect of 5.10^{-6}M and 5.10^{-5}M. The histograms show the mean increase in efflux rate during the 10-min exposure to the drug over the concentration range and they are expressed as a percentage of the control rate of efflux (the average of the previous 5 values)

detrusor from normal Landrace bladders and unstable human bladder in Figure 9.

Discussion

In this report we have demonstrated that cromakalim can suppress the spontaneous activity of pig and human detrusor *in vitro* without compromising the ability of the tissue to respond to activation of the intrinsic nerves, or contract in response to the application of agonist drugs.

The drug increases the electrical conductance of the detrusor smooth muscle cell membrane and causes a pronounced hyperpolarisation to values approaching the estimated K$^+$ equilibrium potential, results which would occur if the drug caused an increase in K permeability of the membrane. An increase in K permeability is also strongly suggested by the flux studies, which show that the drug increases the rate at which K$^+$ ions move both into and out of the cells. It is interesting to note that the K efflux from unstable detrusor is more sensitive to the drug than that from normal detrusor. This mechanism of action of cromakalim is consistent with that reported for other smooth muscles, in which it has been shown to act by activation of K channels (Allen *et al.*, 1986; Weir and Weston, 1986a, b; Quast, 1987).

The hyperpolarisation of the cell membrane results in the supression of the spontaneous electrical and thus mechanical activity of the bladder. In normal bladders, spontaneous activity of the detrusor is not apparent in cystometric recordings, but in unstable bladders there is clear evidence of

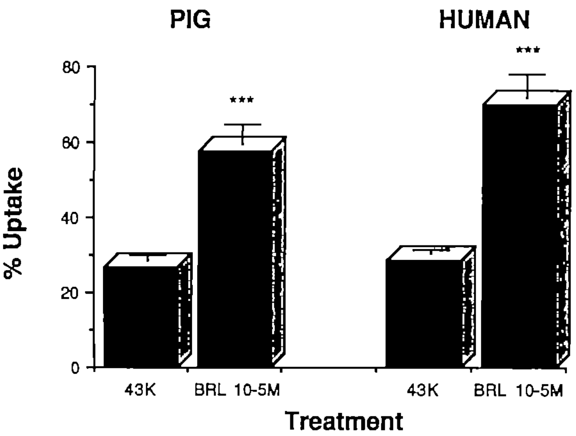

Fig. 9 The effect of cromakalim on the 10-min uptake of $^{43}K^+$ in normal Landrace pigs and unstable human detrusor muscle Uptake is measured as cpm/mg of wet wt. as a percentage of the counts in the uptake solution (cpm/mg), n = 6 for each column shown.

contractile activity, although at present what initiates these contractions is not known. *In vitro* strips of muscle from unstable bladders demonstrate a pattern of activity in which a degree of tetanic fusion and a maintained tone is observed. This pattern of spontaneous activity differs from that seen in stable bladders and suggests that instability is associated with a functional change in the smooth muscle properties. Similar findings have been reported by Kinder and Mundy (1987) in idiopathic detrusor instability and hyper-reflexic bladders. The demonstration that instability associated with bladder outflow obstruction in the pig (Speakman *et al.*, 1987) and human (Harrison *et al.*, 1987) results in a supersensitivity of the smooth muscles to agonists drugs, also supports the suggestion that the underlying pathology of detrusor instability includes an alteration in the properties of the smooth muscle cells.

It is possible that the unstable contractions seen *in vivo* are caused by a combination of increased excitability of the smooth muscle and better conduction of the electrical impulses. This latter point is supported by the observation that we were able to record extracellular electrical activity using the double sucrose gap in unstable detrusor, but not in muscle from normal bladders. This suggests that the ability of electrical activity to spread from cell to cell is enhanced in the unstable detrusor and might lead to better synchronised responses which could account for the unstable contractions.

Whatever the mechanisms causing instability, a drug that directly inhibits the excitability of the smooth muscle, particularly if it does not compromise the micturition reflex, might be of value in suppressing the unstable contractions associated with detrusor instability. Cromakalim seems to have suitable characteristics. When given intravenously to obtructed pigs, the drug proved to be very effective in abolishing the unstable contractions without preventing voiding.

It should be pointed out that cromakalim is also a potent vasodilator and in our experiments it lowered the blood pressure of the pigs when administered in doses that suppressed the unstable contractions. Recent work (Fox *et al.*, 1987) on normal human volunteers has also shown minor cardiovascular effects with lower doses of cromakalim given orally, due to the relaxant effects on vascular smooth muscle. A clinically useful drug for bladder instability would need to be selective for the detrusor. This could be achieved either by looking for tissue-selective drugs or by using the unique position of the bladder to achieve selectivity pharmacokinetically, since a drug active locally (intravesically) and actively secreted by the kidney might reach the bladder in therapeutically active concentrations after enteral or parenteral administration without reaching an effective concentration in the blood stream.

Acknowledgements

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Vaginal Endosonography in the Post-operative Assessment of Colposuspension

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Summary—Vaginal endosonography has been used to investigate the post-operative results of colposuspension. The anatomical relationships of the bladder neck, proximal urethra and symphysis pubis can be demonstrated with this technique. A successful symptomatic and anatomical result was observed in 29/40 women; 11/40 had persistent or recurrent symptoms at varying intervals after the operation. Four different anatomical configurations were associated with these symptoms, which included "early" and "late" recurrent stress incontinence, persistent incontinence, voiding difficulties and the frequency-urgency syndrome.

Persistent or recurrent urinary symptoms were associated with a variety of anatomical configurations after colposuspension. Vaginal endosonography is a simple and convenient method to investigate the early and late post-operative results of operations for urinary stress incontinence.

Colposuspension is a widely used procedure for the treatment of urinary stress incontinence, with success rates of 90% in primary stress incontinence (Stanton and Cardozo, 1979). Studies have been made of unsuccessful outcomes in order to improve the results of the procedure. The post-operative position of the bladder neck has been assessed in failed cases using video cystourethrography (Dundas *et al.*, 1982) and bead-chain cystourethrography (Hertogs and Stanton, 1985). It was concluded that the level of the bladder neck alone was insufficient to distinguish between success and failure. Urodynamic studies in failed cases have identified a variety of poor prognostic features, including the finding of a "low pressure urethra" that is often a consequence of preceding vaginal surgery (Sand *et al.* 1987).

Galloway *et al.* (1987) described urological and gynaecological complications after colposuspension in a series of 50 women with a mean follow-up of 4.5 years and concluded that "there was an unacceptable number of complications" after the procedure. In this report we describe the post-operative anatomical configuration of 40 women after colposuspension for either primary or recurrent stress incontinence. The anatomical configuration was defined using vaginal endosonography. This new technique is a simple, convenient method for the anatomical assessment of the lower urinary tract (Quinn *et al.* 1988). A range of different anatomical configurations associated with post-operative urinary symptoms was identified.

Patients and Methods

A consecutive series of 40 women who had undergone colposuspension was assessed using vaginal endosonography. The clinical details of the patients are given in Table 1. The operations were performed by both gynaecological and urological surgeons. No specific anatomical result appeared to be related to either specialty or seniority.

Vaginal endosonography was performed in the recumbent position with a comfortably full bladder (minimum volume 200 ml), using a high frequency endoprobe (Bruel & Kjaer 8537) together with an ultrasound scanner (Bruel & Kjaer 1846). All examinations were recorded on U-matic videotape

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Table 1 Characteristics of 40 Patients after Colposuspension

Age (+SD) (years)	47 0 (+18.3)	(range 33–75)
Parity (+SD)	2.3 (+0.9)	(range 1–5)
Follow-up (+SD) (years)	2 1 (+1 4)	(range 0 25–8)
Previous surgery:	11 anterior colporrhaphies 1 teflon injection	
Concomitant surgery	5 hysterectomies	

and selected frames were transcribed to X-ray film. Pre-operative investigations included either urodynamic studies or endosonography or both. Urodynamic studies were performed in 17 women before the operation and post-operatively in 6 women with persistent or recurrent urinary symptoms. In 10 patients pre-operative endosonography was performed in addition to the post-operative investigation; 8 of the 10 patients had a successful outcome; 1 developed recurrent stress incontinence 3 weeks after the procedure and 1 developed debilitating frequency and urgency despite having had a stable bladder prior to the procedure.

A successful result was achieved in 29 women (72.5%) and 11 (27.5%) either had persistent urinary symptoms or developed new urinary symptoms following the procedure. Details of the patients with an unsuccessful procedure are given in Table 2.

Table 2 Mean Position of the Radiological Bladder Neck Relative to the Inferior Border of the Pubis

	Vertical (*mm*)	*Horizontal* (*mm*)
Successful outcome (n = 29)	19.0	5 7
Unsuccessful outcome (n = 11)	15.8	8 7

Results

The final position of the radiological bladder neck relative to the inferior border of the symphysis pubis in 29 women with a successful outcome is shown in Figure 1. The mean position of the bladder neck relative to the inferior border of the symphysis pubis in this group was 19 mm above the inferior border of the pubis in this group and 6 mm lateral to this landmark (Fig. 1, Table 2). An explanation of the anatomical configurations is shown in the legend and accompanying line drawings. The longitudinal axis of the patient is represented by the diagonal line shown in Figure 2B and is the same in all scans.

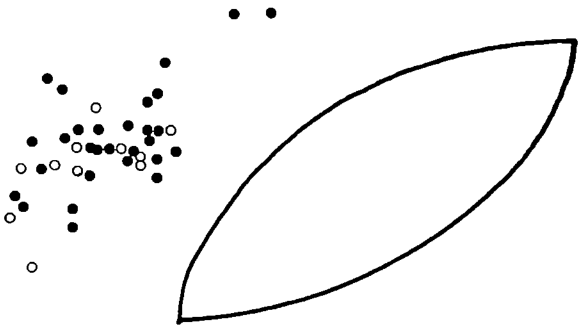

Fig. 1 Position of the radiological bladder neck relative to the inferior border of the pubis ●=Successful outcome ○= unsuccessful outcome.

Four different anatomical configurations were seen in the 11 women who had an unsuccessful result (Figs 3–7). The post-operative urinary symptoms included "early" recurrent stress incontinence in 2 women (Fig. 3), "late" recurrent stress incontinence in 4 (Figs 4 and 5), persistent stress incontinence in 2 (Fig. 6), the frequency-urgency syndrome in 2 (Fig. 7) and voiding difficulties in 1.

Recurrent stress incontinence

Recurrent stress incontinence (RSI) occurred in 2 situations: either early in the post-operative period (within 4 weeks) in 2 patients, or later (with the onset of menopausal symptoms) in 4.

In 1 of the 2 women with RSI in the immediate post-operative period, the diagnosis was confirmed by endosonography. The initial post-operative scan showed an elevated bladder neck (Fig. 2). At 4 weeks she reported recurrent symptoms of stress incontinence following a chest infection. Repeat endosonography confirmed that the bladder neck was no longer supported (Fig. 3). The diagnosis of stress incontinence in the 4 post-menopausal patients was established by endosonography where, despite evidence of an "intact" colposuspension by digital vaginal examination and ultrasound scan (Fig. 4), there was opening and descent of the bladder neck during a cough (Fig. 5). The finding of RSI was confirmed by urodynamic studies in 3 of the 4 patients.

Persistent incontinence

In 2 women who described only minimal improvement in their symptoms following colposuspension, post-operative endosonography showed the bladder base to be indented by the vaginal fornices with the vertical position of the bladder neck unchanged

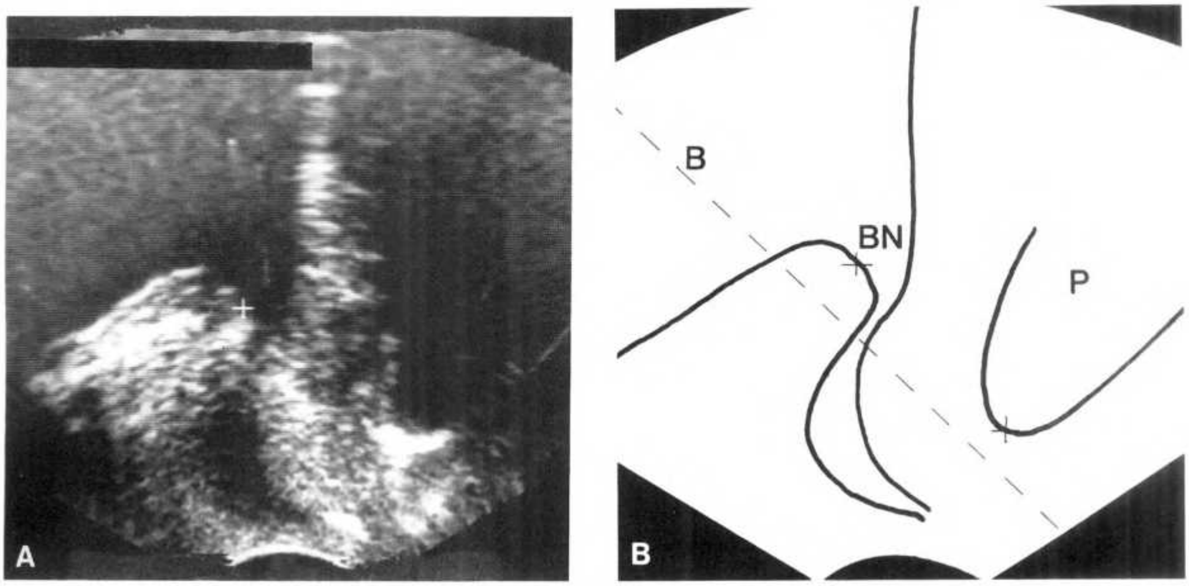
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Fig. 2 (A) Anatomical appearances following successful colposuspension. (B) Same patient. Note that in all scans the longitudinal axis of the patient (dotted line) runs from the top left hand corner to the bottom right hand corner of the image. P = pubis. B = bladder. BN = radiological bladder neck.

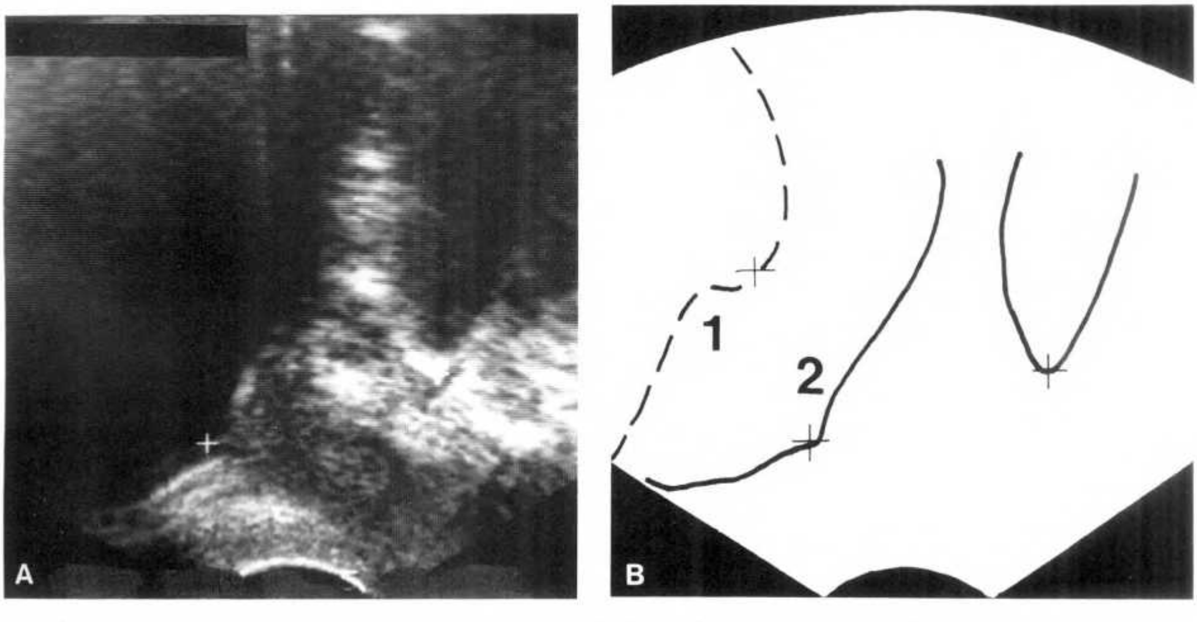
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Fig. 3 (A) "Early" recurrent stress incontinence occurring within 4 weeks of colposuspension. (B) Same patient, showing the immediate post-operative position of the bladder neck (1) and the position at 4 weeks (2).

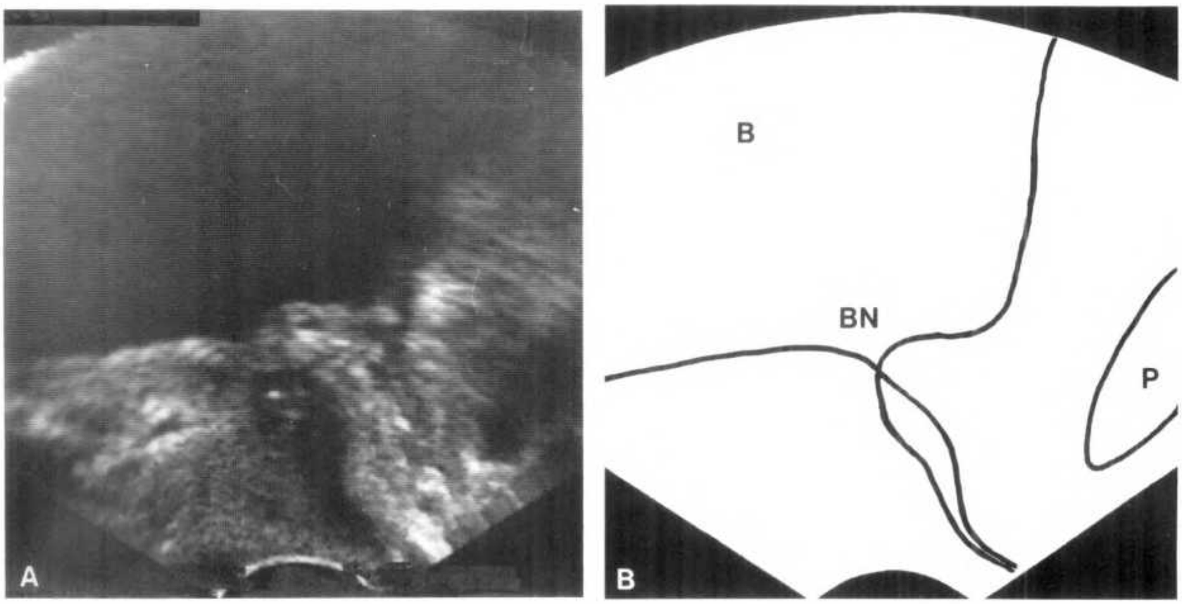

Fig. 4 (A and B) "Late" recurrent stress incontinence in the early post-menopausal years—resting position illustrating an "intact" colposuspension.

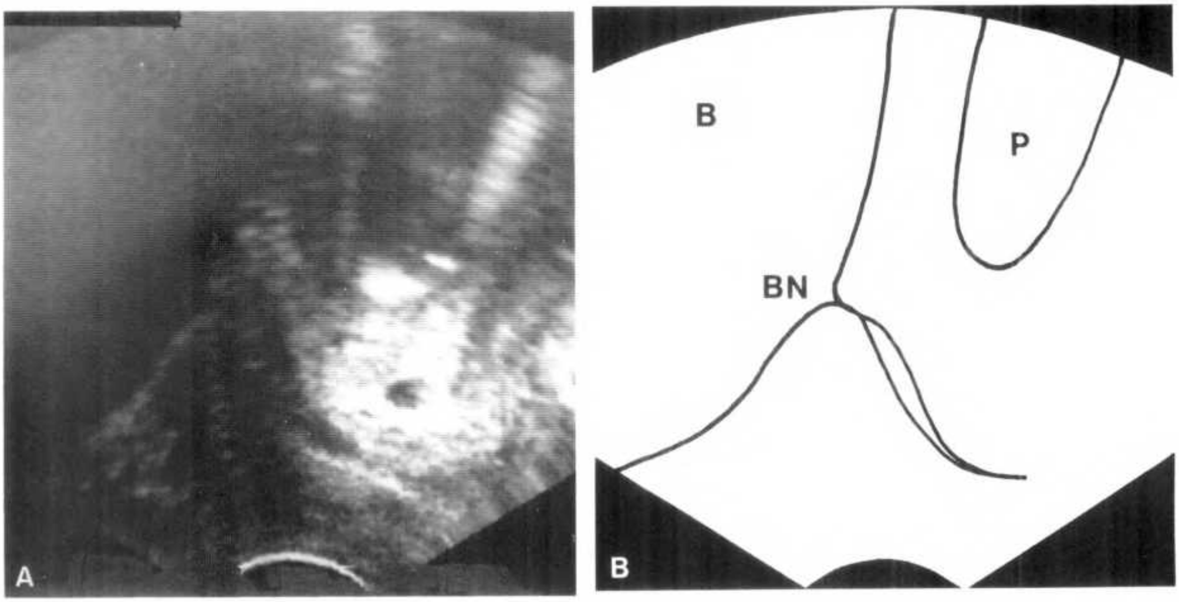

Fig. 5 (A and B) Same patient as in Figure 4 with marked descent of the bladder neck during a cough. Urodynamic studies confirmed stress incontinence.

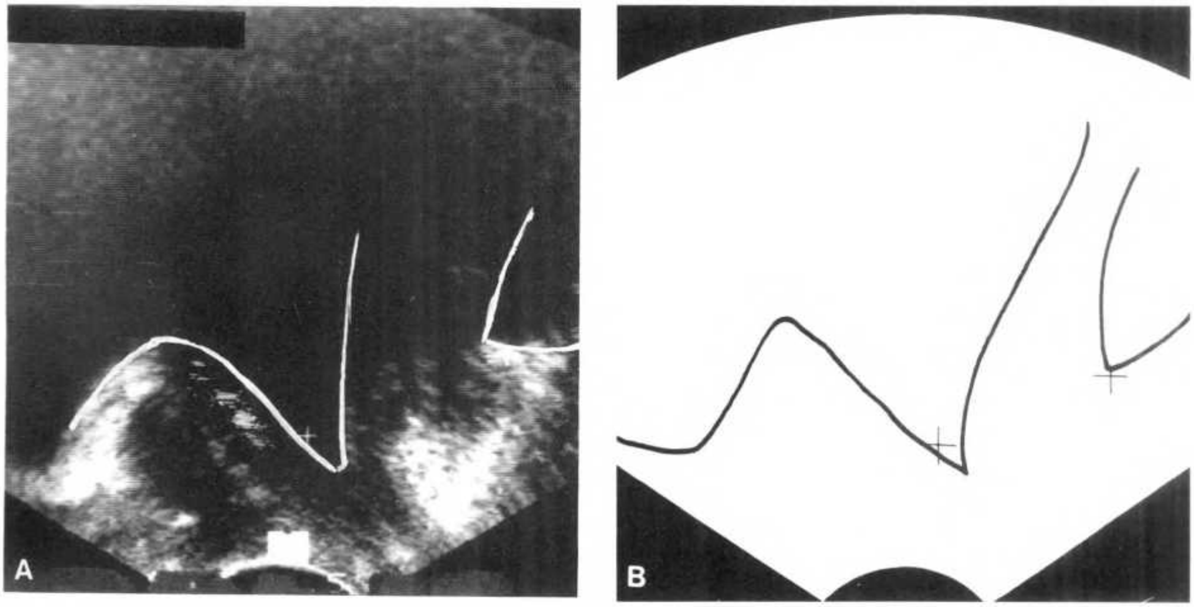

Fig. 6 (A and B) Persistent stress incontinence despite colposuspension. The vaginal fornices indent the base of the bladder rather than elevate the bladder neck.

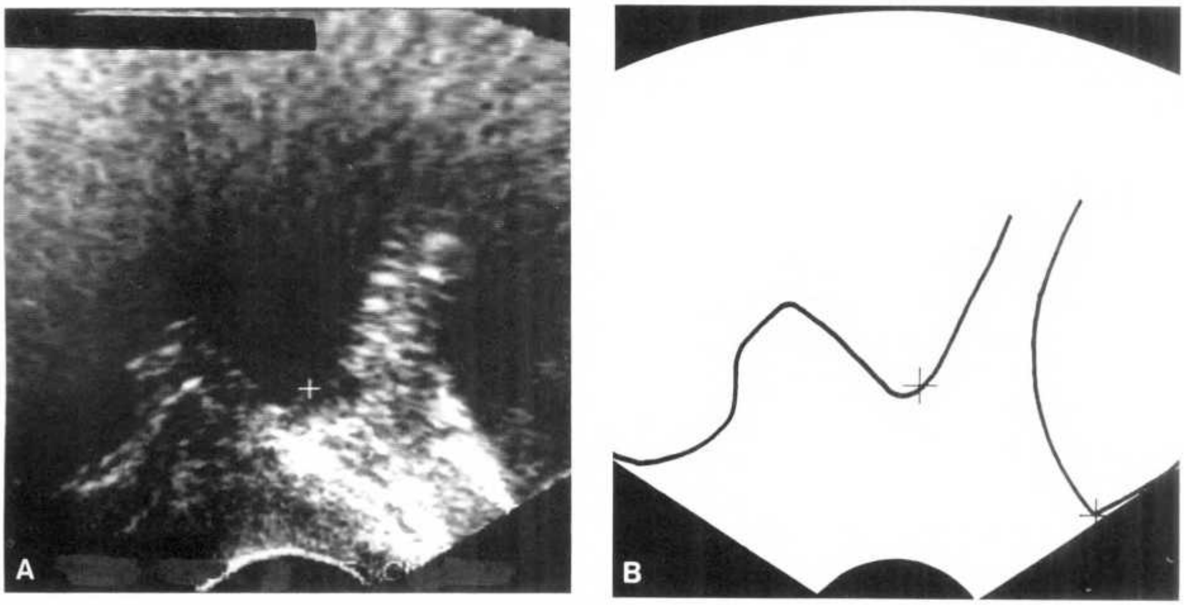

Fig. 7 (A and B) Frequency-urgency syndrome—the vaginal fornices indent the base of the bladder.

from its pre-operative position. During a cough there was persistent opening and descent of the bladder neck (Fig. 6).

Frequency-urgency syndrome

Two women reported persistent frequency and urgency for a minimum of 6 months following colposuspension, neither having described these symptoms before the operation; 1 had pre-operative urodynamics that showed no detrusor instability but neither would agree to post-operative urodynamic studies. Endosonography in both cases showed indenting of the base of the bladder by the vaginal fornices (Fig. 7) with the bladder neck supported above the level of the inferior border of the symphysis pubis.

Discussion

Colposuspension alters the anatomy of the female lower urinary tract by elevating and supporting a displaced bladder neck and proximal urethra. This report confirms the conclusion of Hertogs and Stanton (1985) that "surgical failure after colposuspension usually has an anatomical basis: failure to achieve, or maintain, a correct position of the proximal urethra."

Vaginal endosonography is an effective and acceptable technique for assessing the anatomy and function of the bladder outlet. Other methods such as bead-chain cystourethrography or videocystourethrography are less acceptable to the patient and do not demonstrate the anatomical variations shown by vaginal endosonography. This study confirms that the absolute position of the bladder neck does not discriminate between the success or failure of colposuspension.

The mechanism of success of colposuspension has been suggested as either a repositioning of the bladder neck and proximal urethra or, by elevating and angulating the bladder neck, the creation of a degree of "obstruction". Whatever the basis of success, the anatomical variations described in this report emphasise the importance of correct placement of the sutures so that the vaginal fornices elevate the bladder neck rather than indent the trigone, in order to avoid persistent incontinence or the frequency-urgency syndrome. The correct siting of the sutures may be confirmed by per-operative endosonography. The observation that women in the early post-menopausal years may suffer from recurrent stress incontinence despite a protracted symptom-free period since their primary procedure and an intact repair, requires further study. Other suprapubic procedures may be susceptible to this late complication.

Vaginal endosonography is an effective method for the post-operative assessment of colposuspension. We have shown that the position of the bladder neck after colposuspension does not discriminate between success and failure, that unsuccessful colposuspension is associated with a variety of anatomical configurations, and that recurrent stress incontinence in the early post-menopausal years may be a late feature of colposuspension.

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Is Grade or Stage of Primary Importance in Determining the Outcome after Radical Prostatectomy for Disease Clinically Confined to the Prostate?

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Summary—A series of 145 patients with T1–2N0M0 prostatic carcinoma underwent radical prostatectomy. Specimens were analysed by Gleason sum and categorised according to whether the disease was organ-confined, specimen-confined or margin-positive. The failure of treatment was indicated by elevation of acid phosphatase, by the appearance of biopsy proven local disease or distant nodal disease, or by parenchymal or nodal disease by any imaging modality. Analysis of the data demonstrated that the outcome of surgical intervention was related to the anatomical extent of disease. The Gleason sum was related to the extent of disease and predicted the probability of disease outside the organ of origin.

It has long been our impression that the histopathological grade of the primary tumour is less important in predicting the outcome after radical surgery than is the microanatomical distribution of disease, but that histopathological grade is important in predicting the probability that the disease is either organ-confined or not confined to the prostate. To test this hypothesis we studied the failure patterns of patients as a function of the local distribution of disease and as a function of the Gleason histopathological sum of the primary tumour.

Patients and Methods

Between January 1973 and December 1982, 145 patients with acid phosphatase negative, T1–2N0M0 prostatic carcinoma underwent radical prostatectomy (Paulson *et al.*, 1986). Node-negative or node-positive disease was determined by staging pelvic node dissection, was accomplished by removing all of the node-bearing material and the triangle subtended by the external iliac vasculature, the pelvic floor and the hypogastric vasculature. The node-bearing tissue in this triangle, including that surrounding the obturator nerve, was resected *en bloc*. The resected prostatic specimens were assigned a final Gleason sum and reviewed as to whether the disease was organ-confined, specimen-confined, or margin-positive. All patients were followed up at 3-monthly intervals for the first year and at 6-monthly intervals thereafter with physical examination, acid phosphatase determinations, and periodic chest and full pelvic X-rays. All patients underwent once-yearly isotopic bone scans unless an elevated acid phosphatase indicated metastatic disease prior to that time. Failure of the initial treatment was indicated by an elevation of acid phosphatase, by the appearance of biopsy-proven localised disease or distant nodal disease, or by parenchymal or bony disease by any imaging modality. No patient received adjunctive androgen deprivation therapy unless metastatic disease was confirmed. NED survival rates using time-to-first-evidence of treatment failure were compared by Kaplan Meier actuarial analysis (Kaplan and Meier, 1958). A univaried analysis of Gleason sum and distribution of disease and a multivariate analysis of Gleason sum after controlling for anatomical distribution of disease, and *vice versa* was performed.

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Results

The median follow-up of the 145 patients was 4.98 years. Details of survival and disease-free intervals for the entire population are presented in Table 1 and Figures 1 and 2.

Table 1 Survival and Disease-free Intervals for all Patients

Survival (N = 145)			*Disease-free (N = 145)*		
Years at risk	*% surviving*	*No. at risk*	*Years at risk*	*% NED*	*No at risk*
5	95.2	70	5	84.6	68
7	92.94	34	7	72.4	29
10	92.48	6	10	61.98	4

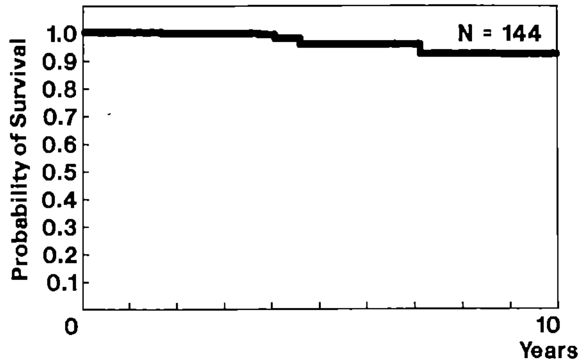

Fig. 1 Survival of patients at risk (Kaplan–Meier (KM) projection)

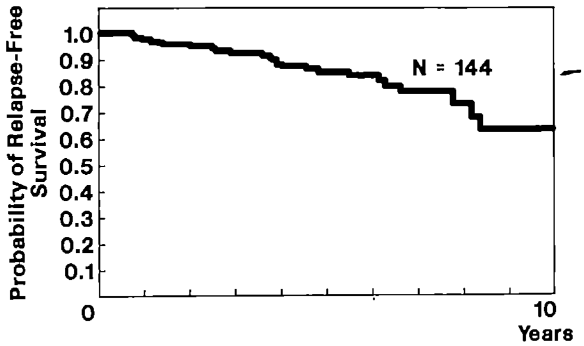

Fig. 2 Disease-free survival of patients at risk (KM projection)

A comparison of tumours that were organ-confined or not confined to the prostate showed little difference in survival but a distinct difference in the disease-free intervals (Table 2, Figs 3 and 4).

Table 2 Survival and Disease-free Intervals in Organ-confined Tumours and those not Confined to the Prostate (N = 145)

Organ-defined disease (N = 89)			*Disease not confined to the prostate (N = 56)*		
Years at risk	*%*	*No at risk*	*Years at risk*	*%*	*No. at risk*
Survival					
5	95.46	37	5	94.5	23
7	93.06	23	7	94.5	11
10	92.06	3	10	94.5	3
Disease-free					
5	92	45	5	70.6	18
7	80.1	14	7	62.16	10
10	61.7	2	10	58.0	2

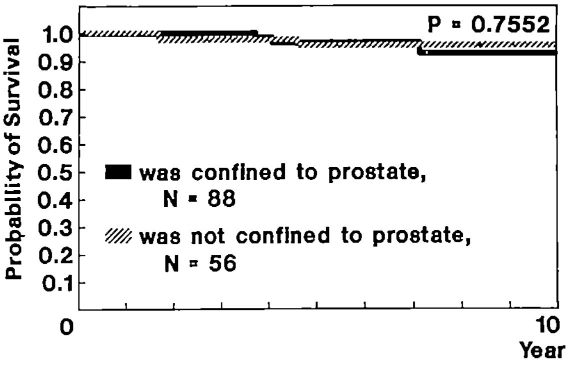

Fig. 3 Survival of patients at risk as a function of disease which was organ-confined or not confined to the prostate (KM projection)

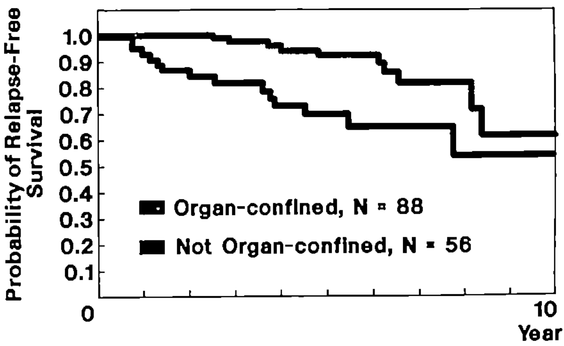

Fig. 4 Disease-free survival of patients at risk as a function of organ-confined diseases versus disease not confined to the prostate (KM projection).

The frequency of Gleason sum distribution, patient failures and time-to-failure in years is given in Table 3 and Figure 5.

Table 3A Radical Prostatectomy in Organ-confined Tumours (n = 89)

Gleason sum	*Frequency no (%)*	*Failures no (% total)*	*Failures % Gleason sum*	*Years to failure*
0	8 (9)	2 (2 5)	25	2 5, 6 4
2	2 (2)			
3	0			
4	14 (16)			
5	18 (20)	2 (2.5)	11	4 1, 4 9
6	27 (30)	2 (2 5)	7	3 8, 8 4
7	10 (11)	1 (1 2)	10	2 9
8	6 (7)	2 (2 5)	25	6 5, 6 7
9	4 (5)	1 (1 2)	25	8 6

Note Gleason grade 0 documents 4 tumour-negative specimens and 4 specimens in which Gleason sum was not available

Table 3B Radical Prostatectomy in Tumours not Confined to the Prostate (n = 56)

Gleason sum	*Frequency no (%)*	*Failures no (% total)*	*Failures % Gleason sum*	*Years to failure*
0	1 (1 8)	1 (1 8)	100	1.3
2	0			
3	0			
4	4 (7.1)	2 (3.9)	50	1 1, 4 7
5	8 (14 3)	2 (2 5)	11	4 1, 4 9
6	14 (25 0)	3 (5.7)	21	3 8, 5 7, 8 0
7	16 (28 6)	1 (1 8)	6 2	0 7
8	5 (8 9)	3 (5 7)	60	0 9, 1.4, 2 7
9	7 (12 5)	3 (5 7)	42	0 7, 3 7, 3 9
10	1 (1 8)	1 (1.8)	100	2 6

Note· Gleason sum 0 documents a specimen in which the Gleason pattern was not determined

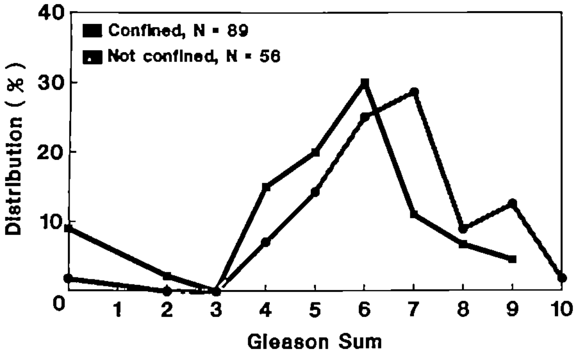

Fig. 5 Frequency of the Gleason sum distribution as a function of organ-confined disease versus disease not confined to the prostate Note that the organ-confined disease shifts towards the lower Gleason sum and that disease not confined to the prostate shifts towards the higher Gleason sum

The time-to-failure analysis as a function of seminal vesicle extension is presented in Table 4 and Figure 6.

Table 4 Seminal Vesical Extension

No (N = 114)			*Yes (N = 30)*		
Time to failure (years)	*% not failing*	*No at risk*	*Time to failure (years)*	*% not failing*	*No at risk*
5	89 4	53	5	64 8	9
7	81 0	23	7	52.9	5
10	65 6	3	10	45.5	1

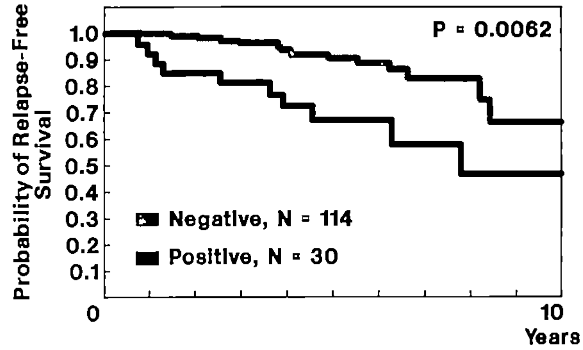

Fig. 6 Probability of relapse-free survival after radical prostatectomy as a function of seminal vesicle extension or no seminal vesicle extension (KM projection).

The frequency of Gleason sum distribution for seminal vesicle negative and seminal vesicle positive disease is given in Table 5 and Figure 7. Seventeen patients with a Gleason sum 5–7 (19%) had seminal vesicle extension while 9 of 23 patients with a Gleason sum 8–9–10 (39%) had seminal vesicle extension (Fig. 8).

An analysis of the Gleason sum distribution between organ-confined tumours and those not confined to the prostate showed that the higher Gleason sum tumours segregated according to local tumour extension ($P < 0.001$) (Table 6). A similar analysis of the Gleason sum distribution of the organ-confined group with respect to failure or no failure predicted that the higher the Gleason sum, the greater the probability of failure (Table 7). The difference between groups was statistically significant ($P = 0.042$).

Univaried analysis of failure as a function of the Gleason sum produced a P value of 0.002 while a univaried analysis of failure as a function of disease that was not confined to the prostate produced a P

Table 5 Seminal Vesical Tumours

Gleason sum	*Frequency no (%)*	*Failure no. (%)*	*Years to failure*
Negative (N=114)			
0	7 (6.1)	2 (6.1)	2.56, 6 35
2	2 (1.8)		
4	15 (13 2)		
5	23 (20 2)	2 (41.2)	4.14, 4 96
6	34 (29 8)	4 (71.1)	3.8, 3.9, 5.6, 8.4
7	19 (16 7)	2 (87.7)	0.7, 2.9
8	8 (7.0)	3 (94.7)	2 6, 6 5, 6 8
9	6 (5.3)	1 (100 0)	8 6
Positive (N=30)			
0	1 (3.3)	1 (3 3)	1 3
4	3 (10.0)	2 (13.3)	1.2, 4.7
5	3 (10.0)		
6	7 (23.3)	1 (46 7)	8 0
7	7 (23 3)		
8	3 (10 0)	2 (80.0)	0 9, 6 5
9	5 (16.7)	3 (96.7)	0 7, 3 7, 3 9
10	1 (3.3)	1 (100 0)	2 6

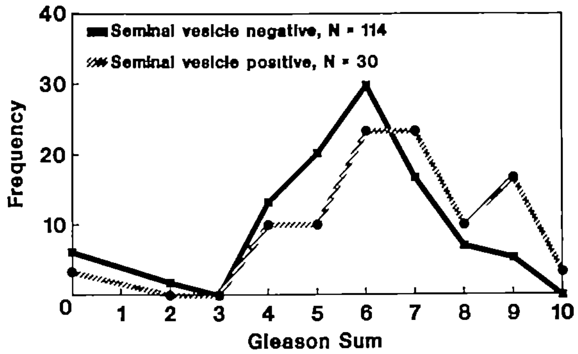

Fig. 7 Distribution frequency of the Gleason sum as a function of seminal vesicle negative versus seminal vesicle positive disease. Note the shift towards the lower Gleason sum for seminal vesicle negative patients and the shift towards the higher Gleason sum for seminal vesicle positive patients.

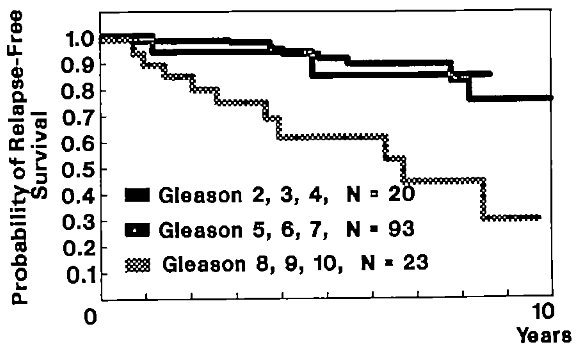

Fig. 8 Probability of relapse-free survival after radical prostatectomy as a function of low, intermediate or high Gleason sum disease (KM projection).

Table 6 Analysis of Gleason Sum Distribution

Group	*Size*	*Mean*	*Median*	*Mode*	*S.P*
Confined	81	5 75	6	6	1 46
Not-confined	55	6.64	7	7	1 47

($P<0.001$)

Table 7 Failure Rates in Organ-confined Tumours

Gleason sum	*Rate of failure*
2, 3, 4	0% (0/16)
5, 6, 7	7% (5/55)
8, 9, 10	30% (3/10)

value of 0.014, indicating that a Gleason sum was a better indicator of failure or recurrence than was anatomical distribution of disease. A multivariate analysis produced a *P* value of 0.0038 when the Gleason sum was adjusted for anatomical distribution of disease, but a *P* value of 0.033 when anatomical distribution of disease was adjusted for Gleason sum.

If patients with tumours not confined to the prostate were divided into specimen-confined and margin-positive groups, Kaplan Meier analysis showed little difference between them (Fig. 9).

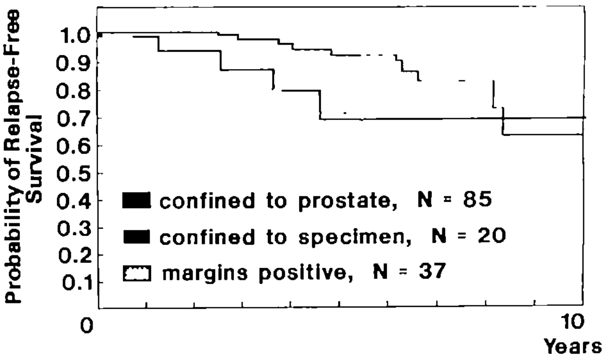

Fig. 9 Probability of relapse-free survival after radical prostatectomy as a function of microanatomical distribution of disease (KM projection).

However, of the 20 specimen-confined patients, 14 had seminal vesicle extension, 4 of whom failed. None of the 6 specimen-confined, seminal vesicle negative patients failed.

Discussion

The data demonstate that the anatomical distribution of disease is a valid predictor of the success or failure of radical surgery in T1–2N0M0 disease. When examined by Gleason sum as a function of organ-confined tumours versus those not confined to the prostate, there is an association between failure and increasing Gleason sum.

Thus the anatomical distribution of disease does not function independently of the histopathological characteristics of the malignancy. While a high Gleason sum does not predict the inability to control the malignancy by surgical means, these high grade tumours demonstrate a propensity for microscopic dissemination not detectable by current staging techniques prior to surgery. The high Gleason sum among patients with disease not confined to the prostate is associated with an increased incidence of seminal vesical extension which equates with a higher probability of failure. The data do not suggest that high Gleason sum patients should be denied radical prostatectomy but do suggest that enthusiasm for radical surgery in these patients should be tempered by a recognition of the benefits of surgical control.

The data demonstrate also that patients whose disease can be removed by expanding the limits of the radical prostatectomy (those with specimen-confined disease can expect a longer disease-free interval than those with margin-positive disease) and that this effect is enhanced by the exclusion of specimen-confined, seminal vesicle positive patients.

Whether this observation argues caution in the enthusiastic pursuit of potency-sparing surgical technique can only be determined by a prolonged follow-up of margin-positive and specimen-confined patients. However, the association of margin-positive disease and failure is sufficiently strong to argue for sacrifice of the periprostatic fascia whenever doubt exists as to the local extent of disease.

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Salivary Testosterone in Prostatic Carcinoma

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Summary—Testosterone concentrations in saliva were measured in 13 patients with prostatic carcinoma after surgical or medical (diethylstilboestrol or Estracyt) orchiectomy. The salivary testosterone values in these patients were significantly lower than in normal males but not significantly different from those in normal females. The salivary testosterone concentrations were measured for 6 consecutive months and did not vary significantly from month to month.

The results suggest that the measurement of salivary testosterone concentrations could be useful in evaluating the androgenic function of patients with prostatic carcinoma after medical or surgical orchiectomy.

The measurement of testosterone in saliva is a non-invasive technique and patients find little difficulty in collecting the samples at home and sending them by mail to the reference laboratory (Riad-Fahmy *et al.*, 1982).

There have been previous reports of the measurement of salivary testosterone in normal men and women (Navarro *et al.*, 1986a), in hirsutism (Villabona *et al.*, 1986; Ruutiainen *et al.*, 1987; Navarro *et al.*, 1987d) and on its relationship with total and free plasma testosterone (Navarro *et al.*, 1986b, 1987a).

Patients and Methods

A study was made of 13 patients aged between 59 and 80 years (66 ± 5, mean ± SD) with moderately or well differentiated prostatic carcinoma. All patients underwent either bilateral surgical orchiectomy or medical treatment with diethylstilboestrol (DES) or Estracyt or both. Those with systemic illnesses were excluded from the study.

A control group comprised 25 men aged between 20 and 40 years and 72 women aged between 20 and 55 years who had no history of serious illness and who were receiving no medication.

Saliva was collected by spitting into disposable plastic tubes and providing volumes of 1 to 2 ml in 5 to 10 min at 09.00 h on the same day of each month for 6 consecutive months following treatment. Six samples were excluded because of technical problems; some samples were collected by the patients at home and posted to the laboratory. All samples were centrifuged immediately and stored at −80°C prior to processing.

Serum was collected into glass tubes by venepuncture at 09.00 h on the same day as the saliva samples were taken. The serum was also stored at −80°C until processing.

Serum testosterone was measured in its basal state and after 6 months using a commercial RIA kit (Farmos Diagnostica, Oulansolo, Finland) according to the manufacturer's instructions. Salivary testosterone was measured in the same way as the serum testosterone. The intra- and inter-assay coefficients of variation were 8.9 and 12% respectively. Mann Whitney's and Wilcoxon's tests were used for statistical analysis of the results.

Results

The salivary testosterone values in the orchiectomised group (both medical and surgical) were 3.3 ± 1.9 ng/100 ml (X ± S); this was significantly lower ($P < 0.001$) than in normal males (9.9 ± 2.8 ng/100 ml) but similar to the values obtained in normal females (3.1 ± 1.1 ng/100 ml) (Fig. 1). There were no significant differences in the monthly values

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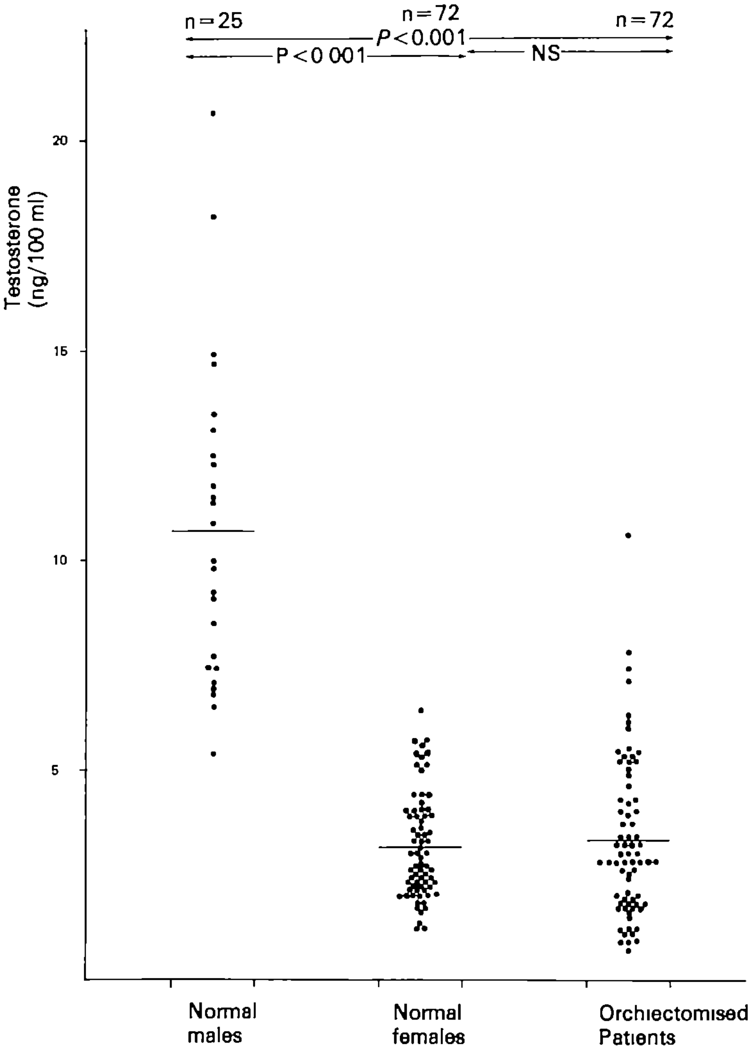

Fig. 1 Salivary testosterone values in orchiectomised patients (both medical and surgical), normal males and normal females A significant difference was found between orchiectomised and normal male patients ($P < 0.0001$). No significant difference was noted between orchiectomised and normal female patients. NS = not significant.

(Fig. 2). The overall correlation, before and after treatment, between serum and salivary testosterone values was $r=0.62$. There was no correlation between testosterone values and the age of the patient.

Discussion

An alternative to the determination of testosterone in serum has been its measurement in saliva. It is accepted that the biological activity of testosterone depends upon the free hormone serum levels but some workers have found a good correlation between testosterone levels in saliva and in serum (both free and total testosterone) (Khan-Dawood *et al.*, 1984; Navarro *et al.*, 1987b).

The saliva is easily collected, even by the patients themselves, and the test is particularly suitable for the long-term follow-up of patients with hypo- or hyper-androgenic conditions (Navarro *et al.*, 1987c). Few studies have been made of salivary testosterone in men with prostatic carcinoma (Walker *et al.*, 1980) and to our knowledge no reports have been published on salivary testosterone in the long-term follow-up of patients with prostatic carcinoma.

Our results show a statistically significant decrease in mean salivary testosterone concentrations

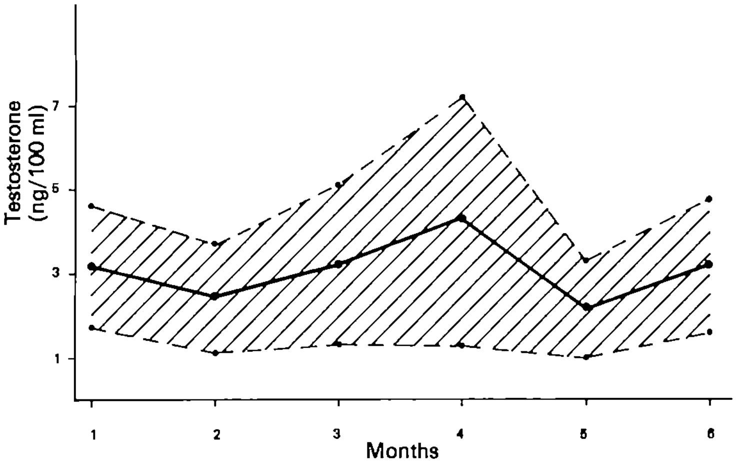

Fig. 2 Salivary testosterone in the follow-up of orchiectomised patients No significant differences were found in salivary testosterone

in men with prostatic carcinoma treated by medical or surgical orchiectomy compared with a control group. These levels did not differ significantly over a 6-month period.

Prospective studies are being carried out on the androgen status of patients with prostatic carcinoma treated with luteinising hormone-releasing hormone agonists.

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The Cost of Bilateral Orchiectomy as a Treatment for Prostatic Carcinoma

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Summary—Advanced prostatic carcinoma may be treated by a variety of methods of hormonal manipulation which affect the production of the male hormones. This can be achieved by surgical means, usually bilateral orchiectomy, or medically, by a number of drugs. One advantage of surgical over medical castration is that it is a once-only procedure. Another factor, which could be considered a major advantage, is the low cost of the surgical procedure. This report outlines the costs involved in treating prostatic carcinoma by surgical castration and compares them with the costs of some forms of medical treatment.

Numerous trials are in progress to evaluate the best forms of hormonal treatment for prostatic carcinoma (Smith, 1987). The appropriate timing for this intervention is also being evaluated (Kirk, 1987). The newer forms of drug treatment are relatively expensive. Drug treatments can be accurately costed within the National Health Service but the cost of surgical treatment, in the form of bilateral orchiectomy, has not been fully evaluated. We have investigated the major contributing factors to the cost of this procedure in our hospital and these costs should be broadly applicable to other NHS hospitals.

Costing a Surgical Procedure

The costing principle which we have adopted is to identify the additional resources involved in surgical treatment (Drummond, 1980). In this case the patient is initially hospitalised for transurethral resection of the prostate and we are concerned with identifying the extra cost of carrying out a bilateral orchiectomy. These costs have been categorised as imposing either a financial cost or an opportunity cost upon the health service. Financial costs arise from, for example, the additional use of disposables in theatre and the cost of anaesthesia. They require direct expenditure on the additional resources and can be directly assessed.

Opportunity costs arise from the extra use of theatre time, additional patient days in hospital and additional hospital admissions. The resources necessary to provide these services are already in place, but their use for patients undergoing orchiectomy deprives other patients of the opportunity to use them. Hence the opportunity cost is defined as the value of these resources in their best alternative use (Drummond, 1980).

Opportunity costs are dealt with separately since they do not result in direct financial expenditure. There is also no possibility of financial savings unless a significant volume of the resource is involved. This is not the case in this situation.

The use of theatre time can be used to illustrate this costing principle. The saving of a small amount of theatre time in any one week would not lead to any financial savings, for example, by allowing reductions in staffing levels. However, if these resources were redeployed to allow other patients to be dealt with, they would have an alternative use. Thus if some theatre time is released, and it is feasible to use this time to treat other patients, the opportunity cost of that theatre time would be measured by the value placed on the improvement in the health of those patients. The notional value of any resources which are released depends,

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therefore, on the extent to which redeployment can take place in practice and the value attributed to treating additional patients. Assuming staffing levels could be permanently readjusted, a financial saving would be made only if a whole session was saved every week.

Surgical Options Costed

Three different treatment options have been costed and all deal with the situation after the initial diagnosis of carcinoma has been made. We have not attempted to cost elective orchiectomy carried out for symptomatic control of metastatic disease.

Option 1. Immediate orchiectomy, carried out at the same time as transurethral resection of the prostate, with frozen section used to confirm the diagnosis of prostatic carcinoma.

Option 2. Orchiectomy as a separate procedure, but during the same admission, on receipt of the pathologist's written report.

Option 3. Orchiectomy as a separate procedure, on receipt of the pathologist's written report, during a second admission.

Option 1 involves the cost of disposables used in performing bilateral orchiectomy, the cost of a frozen section, and costs associated with extending operating time whilst awaiting the pathology report. Option 2 avoids the cost of a frozen section but involves an additional anaesthetic and a second theatre visit. The delay in our experience (1984–1986) adds, on average, an extra 2 days to the hospital stay Option 3 involves the same costs as option 2 plus the costs associated with a second hospital admission, usually lasting 2 days.

Results

In this unit about 70 bilateral orchiectomies are performed each year and the anaesthetic time for this procedure is 20 min. The average time spent in theatre, including recovery time, is 1 h. The costs noted here are not significantly different for either total or subcapsular orchiectomy. The cost of the disposable equipment normally used for this operation is £13.41 (Table 1).

The opportunity cost of a frozen section is £22.50. This includes capital costs and the salaries of trained staff, since these costs are partly dependent on the use of the frozen section service. The financial cost of a frozen section is negligible.

Table 1 Cost of Disposable Equipment for Bilateral Orchiectomy

	(£)
Basic pack (a minor tray from sterile supplies)	3.31
Gowns (triple pack) and Regent gloves	1.81
Sutures	
2 × 759 Chromic catgut (box of 12=£10.91)	1.80
1 × Dexon 4/0 (box of 12=£41.67)	3.47
Scrotal support	1.19
Scalpel blades	
No. 23 (box of 100=£5.19)	0.05
No. 10 (box of 100=£4.99)	0.05
Diathermy pad [£43.32 per box of 25] (*in situ* in option 1)	1.73
Total	13.41

The cost of drugs and disposable equipment for anaesthesia, for a procedure lasting 20 min and using the newer anaesthetic agents, is £5.14 (Table 2) (Astley and Secker Walker, 1982; Lethbridge and Secker Walker, 1986). This figure includes the cost of drugs and disposable equipment only. No account has been taken of capital costs such as equipment or medical and nursing salaries. These costs are unaltered by the addition or deletion of a single operation from a normal operating list and are not considered to be part of the financial cost of the anaesthesia for any individual procedure.

The cost of theatre time for Aberdeen Royal Infirmary in 1982/1983 was £1,047,345 per annum, with direct pay costing £70.04 h. Uplifting these figures by 5% per annum (in line with the Retail Price Index) gives an estimate of present direct pay costs of £81.00 h. The costs of theatre time are constant and not dependent on the procedure being performed. Unless the theatre is closed, no savings are made by not doing a particular operation. If the theatre time involved in the orchiectomies carried

Table 2 Cost of Anaesthetic Disposables and Gases for Orchiectomy

	(£)
3 electrocardiography electrodes	0.58
Venflon 18 gauge cannula	0.72
Syringes and needles	0.18
Sticking plaster	0.01
Airway	0.19
Yankaeur suction catheter	0.72
Gases and drugs (using the newer anaesthetic agents)	2.74
Total	5.14

out annually in this hospital could be redeployed, approximately 24 h of theatre time would be made available.

The average cost of an in-patient day was £101 in 1985/1986. This gives one basis for a notional costing of the additional stay involved in options 2 and 3. It should be stressed, however, that these are opportunity costs. These figures simply provide guidance as to the order of magnitude of costs involved. Additional hospital stays could possibly be provided at less than this average cost, since this is fixed regardless of the scale of activity in the areas that go to make up this average. Thus the costs for hospital stay are likely to be an overestimate of the opportunity cost.

The volume of resources involved is small. If all of the procedures carried out annually involved an extra 2 days in hospital, 140 additional days would be needed. This is equivalent to ½ a staffed bed (at a notional 75% occupancy) or 20 additional cases per year.

The average cost for administration of a short-stay admission is £4.59. Again, this is a notional figure, since most of the cost is for staff time and could not give rise to a financial saving. Some small financial cost, such as postage, would arise but this has not been identified separately.

Using the figures outlined above, the cost for each of these operative options is calculated in Table 3.

The cost of some alternative treatment regimes are shown in Table 4. These have been calculated, where appropriate, as the cost per day and multiplied by 365 days to give a yearly cost. The average monthly cost has been taken as the yearly cost divided by twelve.

Table 3 Cost of Bilateral Orchiectomy

	Option 1 (£)	*Option 2 (£)*	*Option 3 (£)*
Financial costs			
Disposables	11.68	13.41	13.41
Anaesthesia	0.77	5.14	5.14
Total	12.45	18.55	18.55
Opportunity costs (notional value of resources)			
Theatre time*	(81.00)	(81.00)	(81.00)
Hospital stay†	(00.00)	(202.00)	(202.00)
Hospital admission	(00.00)	(00.00)	(4.59)
Frozen section	(22.50)	(00.00)	(00.00)
Total	(103.50)	(283.00)	(287.59)

* Average 1 h

† Average 2 days.

Table 4 Cost* of Alternative Treatment Regimes

	Treatment cost [£]		
	Per day	*Per month*	*Per year*
Diethylstilboestrol (3 mg daily)	0.07	2.26†	27.16
Cyproterone acetate (300 mg daily)	3.41	103.73†	1244.80
Goserelin depot (3.6 mg monthly)	N/A	99.95	1197.00

* Cost to pharmacy at Aberdeen Royal Infirmary

† Cost per year divided by 12

Discussion

If one accepts that there may be little difference between surgical and medical castration in terms of initial control of disease, then cost becomes an important factor in these days of financial constraints. As outlined here, the financial costs of bilateral orchiectomy are as low as those of the cheapest form of drug treatment and are considerably less than those of other available treatment regimes (Table 4). The costs of surgery occur only once, whereas drug costs are cumulative. The relative merits of each of the surgical options above is not under discussion in this report but the financial costs of each are broadly similar.

Although surgical treatment may not incur a large financial outlay, it does represent a use of resources. In this hospital there would be 8 full operating lists available each year if no bilateral orchiectomies were performed. This represents a significant number of patients, *e.g.* those waiting for elective surgery for benign prostatic disease, who could have been treated. However, redeployment of these resources would not in itself cut costs. In addition to theatre time, these patients would also require to use all of the other resources involved in a hospital stay. Some resources might be released by reducing the hospital stay for patients with prostatic carcinoma if no bilateral orchiectomies were performed. However, only 44% of the operations carried out in Aberdeen (1984–1986) fell into options 2 or 3. The extent to which theatre time can be redeployed, without other costs being incurred, will be dictated by local conditions, *i.e.* whether or not beds and other resources can accommodate a small increase in throughput.

Prostatic carcinoma is a common disease which is increasing in incidence (Zaridze and Boyle, 1987). We have shown quite significant differences in the financial and opportunity costs of the treatment options open to surgeons for this disease, and each surgeon must choose the option which seems most appropriate.

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Laparoscopy and the Management of the Impalpable Testis

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Summary—We describe the technique of laparoscopy when seeking to locate an impalpable testis. The procedure was used in 86 boys with unilateral or bilateral undescended testes; of the 103 testes which were sought, 64 were present, 39 were absent and 53 were intra-abdominal. Laparoscopy is useful in the management of the impalpable testis. The information gained from the study is valuable when advising parents of the significance of an impalpable testis. For example, there is a 39% chance it will be absent, a 29% chance that it will be easily placed in the scrotum and a 38% chance that a staged procedure may be necessary.

Laparoscopy is a useful investigative instrument in the management of impalpable testes. The findings at laparoscopy may influence the placing of the incision and in some instances will obviate the need for exploration.

The management of a boy presenting with unilateral or bilateral impalpable testes presents a diagnostic and therapeutic challenge. The diagnostic challenge is to decide if the impalpable organ is present and where it lies. The therapeutic challenge is to decide whether to remove a high testis or to attempt to place it in the scrotum by the most appropriate technique. We presented our preliminary experience in 38 such patients in whom laparoscopy was used to seek the missing testes Malone and Guiney (1984) and now report our findings in a larger series.

Patients and Methods

A total of 86 boys with impalpable testes (age range 2–10 years) were investigated by laparoscopy. The impalpable testis was unilateral in 69 cases and bilateral in 17; the left testis was involved in 45 boys and the right in 24; 64 testes were present and 39 absent.

Technique

Under general anaesthesia a final effort is made to feel the missing testes. If this is unsuccessful, laparoscopy is undertaken using a 5 mm paediatric Storz instrument. If the patient's bladder is palpable above the pubis it is emptied by expression or passage of a catheter. The patient is placed in a slight head down position; the operator should stand on the left of the patient if right-handed and on the patient's right if left-handed. Using a spear-pointed or number 11 scalpel, a 1-mm nick is made in the skin 1 cm below the umbilicus and a small probe cannula inserted through the linea alba. Through this a CO_2 pneumoperitoneum is established. The amount of gas used will vary with the patient but need not exceed 1.5 l. The pneumoperitoneum cannula is left in place, not only for further introduction of CO_2 should this be necessary but also so that it may be used as an examining-retracting probe while viewing the contents of the peritoneal cavity through the scope. To introduce the laparoscope a trocar and cannula is now passed. Once again a sufficiently wide 6-mm incision is made and deepened vertically to incise the linea alba immediately underneath. The incision is gently stretched by inserting a fine straight haemostat and opening the blades. This manoeuvre is important since it ensures the easy passage of the trocar and cannula into the peritoneal cavity and is particularly

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important in small children in order to avoid damage to the abdominal contents. Once introduced, the trocar is removed and the laparoscope passed through the cannula into the peritoneal cavity.

Endoscopic findings

The operator's primary objective is to visualise the internal ring. This is most easily done by placing a guiding finger on the relevant anterior superior iliac spine, which aids orientation of the tip of the laparoscope within the cavity.

In a patient with unilateral impalpable testis it is helpful to compare the normal with the abnormal side. Normally the internal ring can be seen as a slit-like orifice with a vertical crescentic-shaped medial lip of peritoneum.

The testicular vascular leash of artery and vein is seen descending in a lateral retroperitoneal position towards the ring, where it is joined by the whitish vas deferens approaching from the medial aspect of the pelvis, crossing the external iliac artery to join the geniculate vessels as a V at the internal ring. The identification of this V junction is the key to the examination. In the normal situation both limits of the V are seen as positive anatomical structures lying in the retroperitoneum. Difficulty in identifying one or both limbs of the V is indicative of an abnormality.

The most important structure to identify is the testicular vascular leash. When it is seen two features are noted: its direction and its size. Normally the testicular vessels will lead directly toward the internal ring. If the testis lies within the abdomen it may be easily visualised and the vessels and vas seen approaching it. Occasionally, however, the testis lies deeply within the pelvis and is not easily seen. Indeed it may be overlooked or missed unless the vessels are identified and followed to their termination in the pelvic testis. To do this it may be necessary to use the probe-cannula as a retractor of adjacent bowel, to enable visualisation of the testis within the pelvis. The probe-cannula may also be used to flip the testis back up and over the pelvic brim into a site where it is more easily seen. The second feature of the vascular leash is its size, *i.e.* its width and ease of visualisation. The vessels are usually seen to be much smaller on the side of the impalpable testis and can be said to be hypoplastic. The significance of hypoplastic vessels is that when surgically followed to their termination, usually in the inguinal canal, there is no testis present. The vessels and a blind-ending vas deferens are found to lie contiguously. These findings represent the condition known as "the vanished testis". In such instances the vessels and blind-ending vas have been excised and sent for histology. Testicular tissue has never been found in any of the material submitted for examination, although the presence of testicular vessels, even though they be hypoplastic, means that at some time in embryological development a testis was present (Abeyaratine *et al.*, 1969).

If normal sized vessels and vas (on the impalpable side) are seen to pass into the canal, a diagnosis of canalicular testis is made. The accuracy of diagnostic differentiation is now such that when hypoplastic vessels are clearly seen, no further surgical procedure is undertaken. A diagnosis of vanished testis is made and the parents advised accordingly.

The above comments represent the more difficult interpretative aspect of laparoscopy. The findings are often simple, helpful and definitive and the most common finding is that the testis is intra-abdominal. If this is so, it may be sub-classified as follows:

(a) Abdominal. Such a testis is easily seen and lies 1 cm or more distant from the internal ring.

(b) The testis is truly pelvic, not immediately visible, and easily overlooked if the vessels are not followed over the pelvic brim and the probe-cannula used for retraction as previously described.

(c) The testis is just canalicular, in which case the lower pole is seen to be "tucked into" or entering, or just touching the orifice of the internal ring.

A further endoscopic finding is when a vas only is seen, *i.e.* one limb of the V junction. In this event the vas may be seen to end blindly within the abdomen at a point proximal to the internal inguinal ring, or it may curl around the crescentic edge of the internal ring and enter the inguinal canal. In the case of a vas seen without blood vessels it is necessary to seek a testis by examining the normal path of testicular descent by displacing the colon upwards with the probe-cannula and scrutinising the area from the base of the mesentery down to the internal ring. In no such instance has a testis been seen and none found on subsequent exploration on 8 occasions. A diagnosis of testicular absence can be made in such cases regardless of whether the cause was congenital or of the same nature as the vanished testes.

The final, and easily the least common laparoscopic finding, is that there is no evidence of a vas or vessels within the accessible peritoneal cavity.

In this case a diagnosis of true congenital absence of the testis seems justifiable. In the 2 such cases in this series, no testis was found on extensive dissection up to the lower pole of the kidney.

Results

In the 103 testes sought, 53 (51%) were abdominal and their anatomical location is shown in Table 1. The findings in the remaining 50 testes are listed in Table 2.

In all cases these endoscopic findings were confirmed at surgery. Particular note must be made of the 34 instances in which the vas and vessels were seen entering the inguinal canal. At exploration, only 11 testes were found in the canal; in the remaining 23 instances the vessels and vas ended blindly.

Of 103 testes sought, therefore, a testis was present in 64 boys (62%) and absent in 39 (38%).

In only 2 of the 39 absent testes was there no evidence of a vas deferens of testicular vessels. In 14 cases the vas ended blindly in the canal or in the abdomen with no evidence of vessels. These 16 cases, therefore, in which there was no evidence of testicular vessels, could be classified as congenitally absent. In the remaining 23 cases a vas and testicular vessels were identified. The fact that vessels were present at one time means that the testis was also present but it had vanished. With the exception of those with high bilateral intra-abdominal testes, all patients underwent surgical exploration and orchiopexy following laparoscopy.

Table 1 Location of Testes

Sites	*No.*
Within the abdomen and above the pelvic brim	23
Over the brim of the pelvis, *i e* pelvic	11
At the internal orifice of the inguinal canal, *i e* just canalicular	19
Total	53

Table 2 Endoscopic Findings

Sites	*No*
Vas deferens and vessels seen entering the canal canalicular	34
Vas deferens only seen entering the internal ring, no vessels visualised	6
Blind-ending vas seen no testis	8
No vessels or vas seen no testis	2
Total	50

Discussion

Testes which lie within the canal or just at the internal ring can usually be placed satisfactorily in the scrotum by an extended orchiopexy, helped by the placing of a high incision which will permit extensive dissection of the intra-abdominal portion of the testicular vessels. In such cases the length of the vas is not usually a problem. On the other hand, testes which lie within the abdomen or in the pelvic cavity at a distance from the internal ring cannot usually be brought down satisfactorily even with a staged procedure. If they are brought down they develop poorly. In the case of a unilateral abdominal or pelvic testis with a contralateral normal side, we therefore remove the undescended organ if a trial dissection indicates that it will not come down satisfactorily. In cases of bilateral testes detected at laparoscopy, the vas (since it is usually very short) is, in the case of a pelvic testis, the restraining factor in preventing adequate orchiopexy, although exceptions have been encountered.

In a boy with an impalpable testis there is a 38% chance it will be absent; if it is present (the canalicular or just canalicular testis), there is a 29% chance that it will be easily placed in the scrotum; in the remaining 33% (abdominal or pelvic testis), the possibility of a staging procedure or orchiectomy or a vascular transplantation exists.

The high incidence of absence of the testis, when it is not clinically palpable, has been reported by Scott (1982).

Some workers have queried the role of laparoscopy in the management of this clinical problem. While it is clearly not an essential ingredient—in the treatment of patients with unilateral undescended testis—we believe it is a useful additional investigative method. Prior knowledge of the actual location of the testis may guide the surgeon in the placing of his incision, and the use of the high Jones incision (Jones and Bagley, 1979) may achieve successful orchiopexy in an otherwise borderline case. We believe this incision to be preferable to a laterally extended standard groin approach.

In the case of bilateral impalpable testes the laparoscope can make an important contribution to the planning and execution of treatment, particularly with regard to microvascular surgery, although we accept that microvascular transplantation should be attempted only in boys with bilateral high intra-abdominal testes.

Because of hypoplasia of the testicular vessels visualised at laparoscopy, we can now make a firm diagnosis in most patients with a vanished testis in the canal and all of those with blind-ending intra-abdominal vessels or vas. With increasing frequency we do not explore these boys, thus sparing them the discomfort of surgery.

We believe that laparoscopy is useful in the management of the impalpable testis and that it should be used in paediatric surgical units which deal with a large number of possibly cryptorchid boys.

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Circannual Rhythmicity in the Occurrence of Idiopathic Priapism in North-Western India

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Summary—A group of 26 patients who were operated upon for idiopathic priapism between 1972 and 1986 were classified according to the date on which they attended hospital. During the same 15-year period 150 patients with penile cancer were treated and they served as controls.

The data were analysed for circannual rhythmicity (365.25 days = 360° and 0° = 22 December. This revealed a significant circannual rhythmicity in the occurrence of idiopathic priapism, with the acrophase located on 2 August. There was a significantly higher incidence of idiopathic priapism between April and September.

The precise aetiology of idiopathic priapism is not known. The close association between man and his environment not only plays an important role in several physiological functions of the body but also influences the occurrence of various diseases. A circannual rhythmicity has been demonstrated in human male sexual activity (Reinberg and Lagoguay, 1975) and in conception (Ronnike, 1981). A study was therefore undertaken to see if circannual rhythmicity played any part in the occurrence of idiopathic priapism.

Patients and Methods

A retrospective analysis was made of patients with idiopathic priapism treated between 1972 and 1986. The date on which they attended hospital and any aetiological factors were noted from the hospital records. If aetiological factors were found, the patients were excluded from the study. The data were analysed for circannual rhythmicity, taking 365.25 days = 360° and 0° = 22 December (Nelson *et al.*, 1979).

The data were also analysed by Hewitt's rank-sum criterion of seasonality (Hewitt *et al.*, 1971). This is based on the sum of the ranks of r successive months. On the grounds that the chance probability of obtaining the largest possible rank-sum is smallest where $r = n/2$, the rank-sum for 6 successive months is used, where the monthly frequencies have been ranked from 12 (highest) down to 1 (lowest). When no prior hypothesis exists it is necessary to locate the 6-month segment which yields the highest value of the rank-sum. No lower limit on the sample size exists for the rank-sum criterion, except as entailed by the practice of requiring that at least 6 of the 12 months must have non-zero frequencies. A value of the rank-sum equal to or greater than 50 would be regarded as significant at the 5% level.

After locating the 6-month segment which yielded the highest rank-sum, the data were analysed by chi-squared test with Yates' correction (Box *et al.*, 1978) for the same 6-month period. The control group for analysis by chi-squared test consisted of patients with penile cancer treated during the same 15-year period. The chi-squared test was also used for three 4-month periods (January–April, May–August, September–December) and for four 3-month periods (December–February, March–May, June–August, September–November).

Results

Twenty-six patients with idiopathic priapism were operated upon between 1972 and 1986. Their ages

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ranged from 18 to 47 years (mean ± SD = 32.76 ± 7.33 years). During the same period 9 patients with priapism were seen in whom an aetiological factor was found (leukaemia (2 patients), heparin therapy for deep venous thrombosis (1), heparin for haemodialysis (1), phenothiazine therapy (1), alpha blocker for hypertension (1), fractured pelvis (2) and perineal injury with haematoma (1)) and they were excluded from the study.

Cosinor rhythmometry revealed a circannual rhythm in the occurrence of idiopathic priapism ($F_{2,9} = 11.76896$; $P < 0.005$). The acrophase was located on 2 August. The amplitude was 2.29450. Between April and September there were 22 cases of idiopathic priapism and only 4 between October and March (Fig. 1). Hewitt's rank-sum criterion of seasonality showed a significantly higher incidence of idiopathic priapism between April and September (rank-sum 57, $P < 0.05$) compared with the 6-month period of October to March.

During the same 15-year period 150 cases of penile cancer were treated in this hospital. The monthly incidence of penile cancer is shown in Figure 1. The chi-squared test with Yates' correction showed a significantly higher incidence of idiopathic priapism between April and September (Fig. 2) compared with October to March ($\chi^2 = 9.74$; df = 1; $P < 0.01$). When the data were analysed for three 4-month periods (January–April, May–August, September–December) (Fig. 3), a significantly higher incidence of idiopathic priapism was observed between May and August ($\chi^2 = 13.09$; df = 2; $P < 0.01$). Similarly, analysis of the data for four 3-month periods (December–February, March–May, June–August, September–November) (Fig. 4) revealed a significantly higher incidence of idiopathic priapism between June and August ($\chi^2 = 12.74$; df = 3; $P < 0.01$).

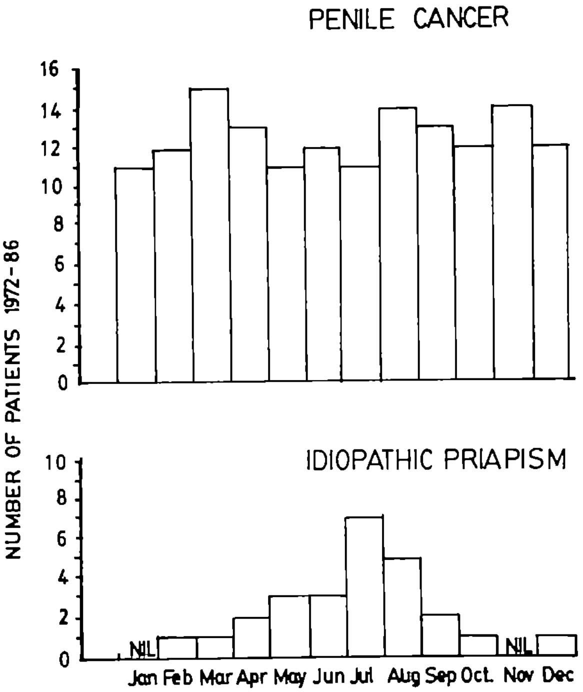

Fig. 1 Monthly incidence of penile cancer and idiopathic priapism between 1972 and 1986.

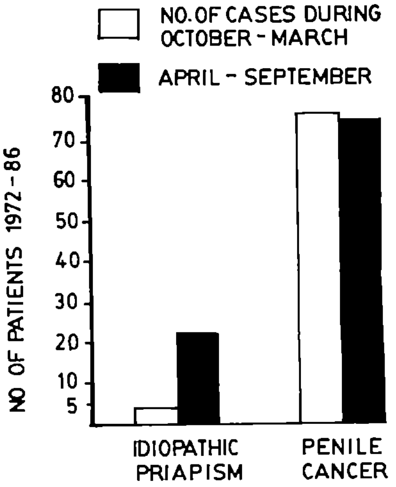

Fig. 2 Incidence of penile cancer and idiopathic priapism during two 6-month periods.

Discussion

Seasonal variations in normal births (Ronnike, 1981), still-births (Slatis and De Cloux, 1967) and

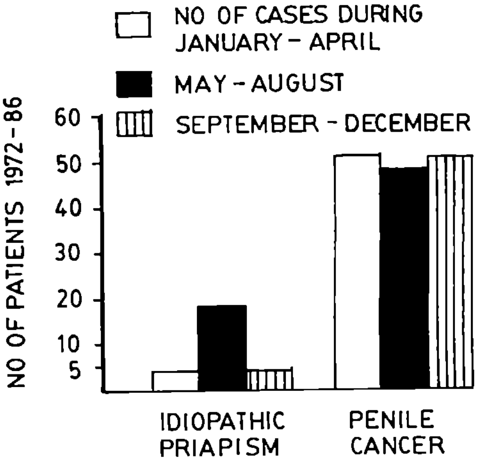

Fig. 3 Incidence of penile cancer and idiopathic priapism during three 4-month periods

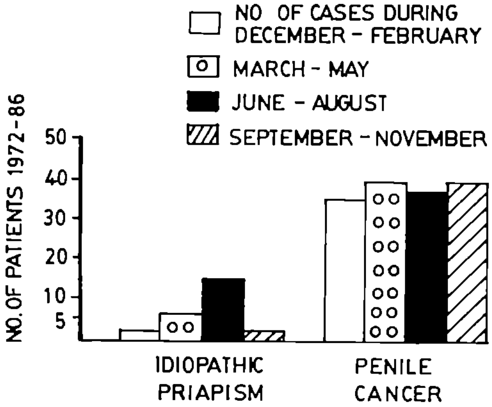

Fig. 4 Incidence of penile cancer and idiopathic priapism during four 3-month periods.

abortions (Koras and Taylor, 1960) have been recognised for several years. Similarly, seasonal variations have been observed in the occurrence of various congenital malformations, infections and other diseases affecting adults such as coarctation of the aorta (Miettinen *et al.*, 1970). It has long been known that several functions related to the excretion of urine as well as diseases of the genitourinary tract undergo not only circadian but also circannual variations. Thus longitudinal studies of urinary excretion show both circadian and circannual variations (Reinberg *et al.*, 1978). The formation of urinary calculi associated with ureteric colic shows a circannual rhythm (Laerum, 1983). An increased incidence of testicular torsion during winter in Dublin (Shukla *et al.*, 1982), the United Kingdom (Newcombe, 1983; Williamson, 1983) and Chandigarh (Malakondiah *et al.*, 1986) has been reported.

A relationship between seasonal changes in sexual hormone secretion, sexual behaviour and sperm production has been described in man (Pinatel *et al.*, 1982). A circannual rhythm in human male sexual activity and plasma testosterone was established in a study carried out in France by Reinberg and Lagoguay (1975). Both plasma testosterone and sexual activity showed an annual peak around October and a trough around May, suggesting that the circannual rhythm of plasma testosterone and human male sexual activity might be related. A similar study of the circannual variation in plasma testosterone and human male sexual activity in India might shed light on the circannual rhythm in the occurrence of idiopathic priapism, as observed in this study.

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We thank past and present Residents, the staff of the Department of Urology and the Central Registration Department, PGIMER, Chandigarh, for their help

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Long-term Follow-up of the MAGPI Operation for Distal Hypospadias

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Summary—Following the introduction of the MAGPI procedure, this operation has become established in the management of distal hypospadias. In our unit 45 boys have been treated in this way and the long-term results have been assessed in 28. The cosmetic result of surgery and the direction of the urinary stream were satisfactory in 27 patients. In all but 2 cases there was partial ventral regression of the urinary meatus when compared with the immediate post-operative appearances.

In the long term, it is our experience that the MAGPI operation does not maintain a terminal position for the external urinary meatus, but the functional and cosmetic results are satisfactory.

In 70% of patients with hypospadias the abnormality is considered to be distal, the external urinary meatus being subcoronal, coronal or glanular (Duckett, 1981). Previously, such cases were not corrected because the abnormality did not affect procreation and the available procedures had high complication rates. Following the description of the MAGPI procedure (meatal advancement and glanuloplasty) by Duckett (1981), interest in the surgical correction of distal hypospadias has been revived. We report our experience with this operation.

Patients and Methods

Between 1981 and 1987, 45 boys underwent a MAGPI procedure. Surgery was deferred until the patients were 2½ years old and any child who presented later had his operation immediately; 20 boys had glanular, 24 coronal and 1 subcoronal hypospadias. In addition, 3 had chordee and 4 had marked penile rotation.

Pre-operatively, all of the parents had two main concerns: the unacceptable cosmetic appearance and the abnormal direction of the urinary stream. In 39 boys the stream was deviated backwards and in the remainder the direction was sideways. In addition, 11 children were noted to spray.

All children underwent the standard MAGPI procedure (Duckett, 1981). In 4 patients penile rotation was corrected with skin flaps at the same time; 6/0 Dexon sutures were used for the meatal advancement and glanuloplasty and the skin was approximated with 5/0 Dexon. The procedure was not carried out when marked chordee was demonstrated by artificial erection.

The first 25 patients had urethral splints inserted at operation and left *in situ* for 5 days, under antibiotic cover. Most were discharged on the sixth post-operative day. The last 20 patients had neither splints nor antibiotics and all but 2 were kept in hospital for 1 post-operative night.

Results

Post-operative complications were minimal but 2 boys (both splinted) required suprapubic aspiration of the urine in the immediate post-operative period and were subsequently able to void around the splint; 3 boys required re-operation, 1 for fistula, 1 for meatal stenosis and 1 to improve the cosmetic appearance. Another fistula closed spontaneously. With these exceptions, all parents expressed satis-

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

faction with the results of surgery at 3 months and the neo-meatus was at the tip of the glans in 40 of the 45 boys.

In order to assess the long-term results of this procedure, all patients were contacted; 28 boys (62%) attended for long-term review between 9 months and 5 years after operation. The mean duration of follow-up was 2.9 years and the interval between surgery and this review was at least 1 year in 26 cases. Pre-operatively, 12 boys had glanular hypospadias, 15 coronal and 1 subcoronal. Of the 28, 17 were splinted post-operatively and the remainder were not.

The parents of all but 1 (who had required re-operation for fistula) remained satisfied with the results of the procedure at late review and were pleased with the direction of the urinary stream, which was forwards in 27 patients; 3 boys still had some spraying of the urinary stream. The cosmetic result was considered satisfactory by the parents of 26 boys.

The significant finding was that in 26 of 28 cases the neo-meatus had partially regressed proximally (Fig.), although no difficulty was encountered with the glanuloplasty at operation. The 2 boys in whom there was no meatal regression both had splints *in situ* in the post-operative period. Pre-operatively, the meatus was glanular in 1 and coronal in the other.

At operation the urethra is supported ventrally by mobilisation and suturing of the glans. This support was absent at review, leaving a "fish mouth" appearance. The meatus did not regress to the pre-operative site in any of the boys. This finding was only evident on careful examination and was not associated with abnormal direction of the urinary stream.

Discussion

Clinically there are two major problems associated with distal hypospadias: the appearance of the penis and the direction of the urinary stream. Other operative procedures (Mathieu, 1932; Mustarde, 1965; Devine and Horton, 1977) have inherent complications such as ischaemia of skin flaps, fistulae and meatal stenosis (Duckett, 1981).

In his original description of the MAGPI procedure, Duckett (1981) proposed its use in hypospadias which was subcoronal or more distal. Furthermore, penile rotation can be corrected by the use of skin flaps so as to rotate the penis in the opposite direction. Minor degrees of chordee are correctable but there is a high complication rate associated with more severe forms of this contracture (44%) (Ozen and Whitaker, 1987).

In common with others (Man *et al.*, 1984; Ozen and Whitaker, 1987), we initially used urethral splinting. However, we have now abandoned this practice since there was no apparent benefit and it was associated with prolonged hospitalisation. Splinting does not confer a significant advantage, regression of the meatus occurring in 15 of 17 splinted patients and all 11 who were not splinted.

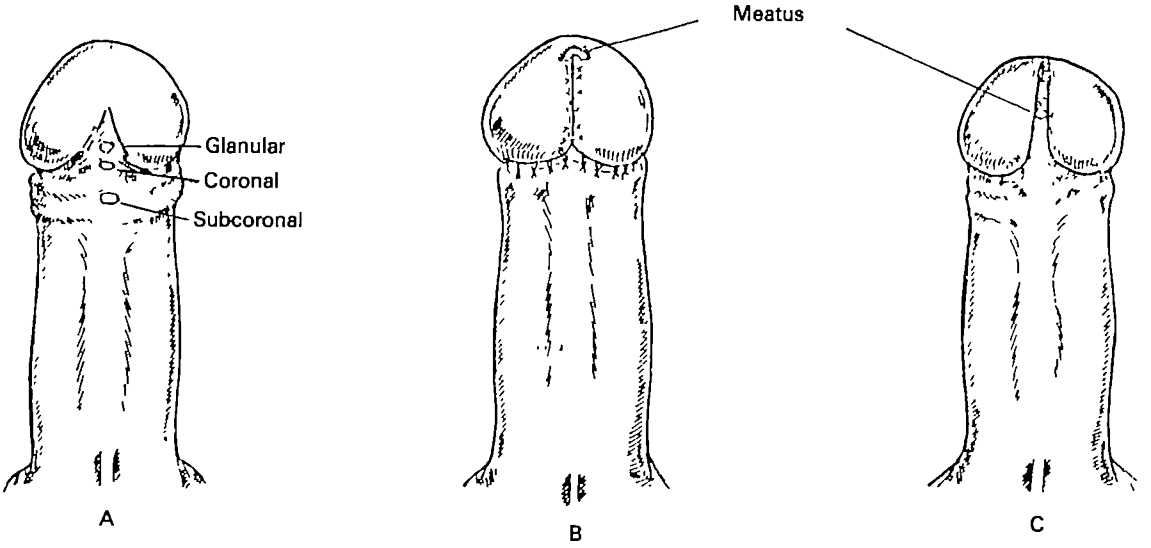

Fig. (A) Possible positions of meatus in distal hypospadias (B) Immediate post-operative appearance (C) Appearance at late follow-up

During the MAGPI repair the bridge of tissue in the subglanular groove is incised longitudinally and sutured transversely in order to advance the meatus. This manoeuvre is the major reason for the improved direction of the urinary stream after a MAGPI procedure and the position of the neomeatus at the tip of the glans is not as critical.

Previously reported series (Man *et al.*, 1984; Ozen and Whitaker, 1987), with a maximum follow-up of 10 and 3 months respectively, showed a terminal meatus in approximately 90% of cases. Our findings at the 3-month review were similar, with a terminal meatus in 89% of the boys. However, at late follow-up the meatus was terminal in only 2 of 28 cases (7%).

Hodgson (1984) considered that the procedure was an "illusion" as the meatus is incorporated into the glans, giving a rounded configuration. Our experience confirms this view but the ventral support afforded to the urethra during the procedure diminishes as growth occurs, resulting in partial meatal regression.

Despite this, the MAGPI procedure offers a reliable technique which improves the direction of urinary flow and the cosmetic appearance of the penis in distal hypospadias. The position finally adopted by the meatus does not appear to be significant in determining the eventual functional result.

Acknowledgement

We are grateful to Miss Delia Simpson for her secretarial assistance.

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Case Reports

Squamous Cell Carcinoma of the Bladder presenting as Vitiligo

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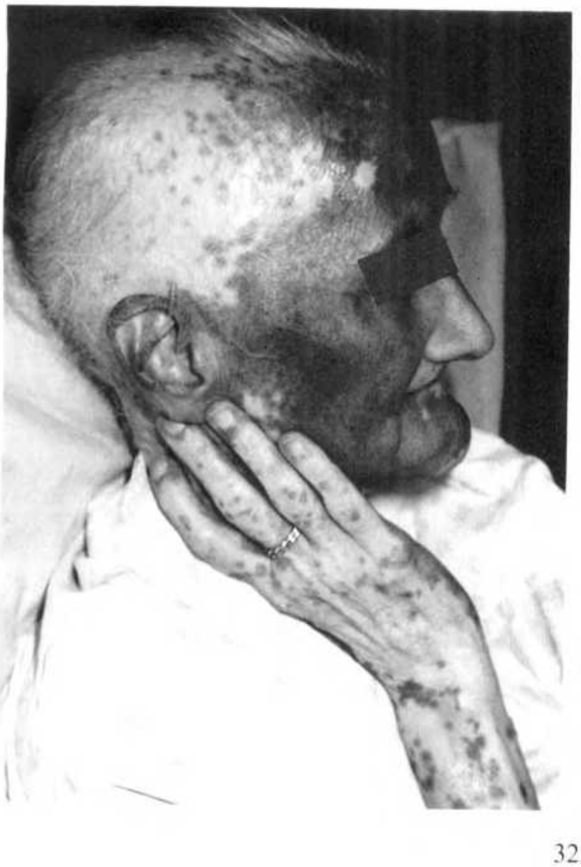
We report vitiligo as a presenting feature of squamous cell carcinoma of the bladder. No such association has previously been described.

Case Report

A 77-year-old Indian female presented with a 9-month history of widespread vitiligo of sudden onset (Fig.) and a 3-month history of weight loss, anorexia, abdominal pain and intermittent pyrexia of unknown origin.

She was found to have a mass in her lower abdomen and was initially investigated for occult tuberculosis. Cytology and culture of several early morning urine samples were normal and intravenous urography showed an atrophic left kidney with a normal right kidney. Cystoscopy and biopsy of the bladder neck were normal. Anti-tuberculous chemotherapy was started empirically.



Since the patient failed to show clinical improvement and then developed haematuria, she was transferred to Northwick Park Hospital for further investigation. On examination she was cachectic, had florid vitiligo and a lower abdominal mass with inguinal lymphadenopathy. Pelvic ultrasonography was inconclusive but repeat cystoscopy and biopsy revealed a T4 squamous cell carcinoma of the bladder. There was no evidence of bladder calculi or urinary schistosomiasis.

Comment

The onset of vitiligo in the elderly has been associated with various neoplasms including adenocarcinoma of the bowel, brain glioma, malignant melanoma and squamous carcinoma of the skin and uterus (Lassus *et al.*, 1972).

Specific skin lesions have not been previously reported with bladder neoplasms. Our patient had vitiligo which first appeared in her 70s. The sudden onset of vitiligo, unusual in the elderly, appeared to coincide with the development of bladder carcinoma.

The possible mechanism of the relationship is interesting. Vitiligo is often associated with organ-specific autoimmune diseases, although no specific anti-melanocyte antibody can be detected. Immune mechanisms are known to be intimately involved with neoplasms of the bladder; it is recognised that local suppression of delayed hypersensitivity may be involved in the spread of transitional cell carcinoma of the bladder (Lamm *et al.*, 1977). This forms the rationale of BCG therapy of superficial bladder carcinoma (Morales *et al.*, 1976).

The association of squamous cell carcinoma of the bladder and vitiligo implies a possible immune basis for some primary bladder neoplasms.

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Epidermoid Cyst of the Testis

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Case Report

A 30-year-old male was referred by his general practitioner with a left-sided, painless testicular swelling. The swelling had been present for 18 months but had recently increased in size. There was no history of trauma or any previous medical intervention. Clinical examination revealed a discrete, non-tender swelling in the lower pole of the left testis. Ultrasound examination showed an irregular echo pattern which confirmed the clinical impression that this was most likely to represent a germ cell tumour. A pre-operative chest X-ray was normal and serum HCG and AFP were within normal limits.

The testis was explored through an inguinal incision. After clamping the cord, the testis was incised and the lower pole found to contain a 3 × 4-cm white homogeneous tumour compressing the normal testicular tissue at its margins (Fig. 1). Macroscopically it was thought to be a seminoma and the testis and cord were excised.

Microscopically the lesion consisted of a cyst, lined with stratified squamous epithelium and containing keratin (Fig. 2). The cyst was well circumscribed and found adjacent to testis, rete testis and epididymis. There was a chronic inflammatory cell infiltrate surrounding the cyst wall but no evidence of a granulomatous reaction which would have suggested rupture of the cyst. The entire lesion was subjected to histological examination and no variation in this structure was identified, thus excluding teratomatous elements. Immunoperoxidase staining for HCG and AFP confirmed the lack of any such elements. The tumour was classified as a benign epidermoid cyst.

Comment

Epidermoid cysts of the testis are rare lesions which are usually confused clinically with testicular germ cell tumours (Price, 1969). The histogenesis of epidermoid cysts in the testis is unclear. They are regarded by some as representing a monodermal development of a teratoma (Price, 1969) and by others as being derived from squamous metaplasia of the rete testis or seminiferous tubules (Halbey, 1961). The absence of HCG and AFP immunoreactivity and the benign nature of these lesions would tend to favour the latter hypothesis.

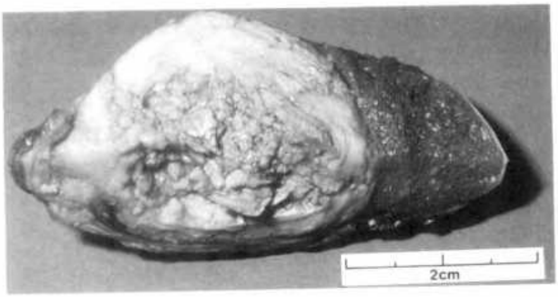

Fig. 1 Gross section of testis.

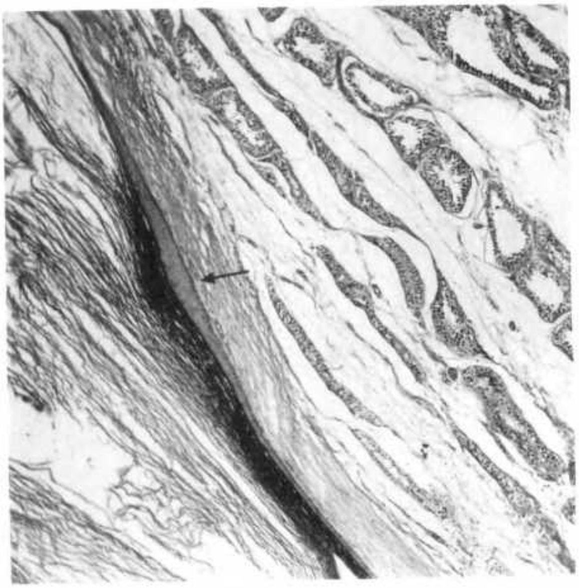

Fig. 2 Section showing compressed testis. Arrow indicates cyst wall. (H & E × 40).

Despite the controversy over histogenesis, there are no recorded cases of recurrence or metastases from simple stratified squamous-lined cysts (Price, 1969). Orchiectomy is normally performed as there is usually clinical doubt as to the nature of the lesion and the full specimen requires to be processed to exclude the lesion being a teratoma.

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Appendicovesical Fistula Presenting as Urethral Stricture

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We describe a patient with an appendicovesical fistula, which is a rare complication of acute pelvic appendicitis. The classic symptoms of pneumaturia and faecaluria, seen in most patients with vesicoenteric fistulas, are usually absent in these cases.

Case Report

V.D., a 20-year-old labourer, was admitted with a periurethral abscess pointing in the perineum. It was drained; 15 days later he developed retention of urine and as an attempt at catheterisation failed, suprapubic cystostomy was performed. He denied any pain in the right iliac fossa or micturition problems prior to this illness.

Examination revealed 2 periurethral fistulas. Routine laboratory investigations were normal except for pyuria and repeated reports of contaminated urine. IVU showed normal upper tracts and a retrograde urethrogram showed an irregular bulbar urethra. Micturating cystography demonstrated dye in the colon as well as the stricture. A diagnosis of colovesical fistula was made. Sigmoidoscopy and barium enema failed to demonstrate the communication with the bladder.

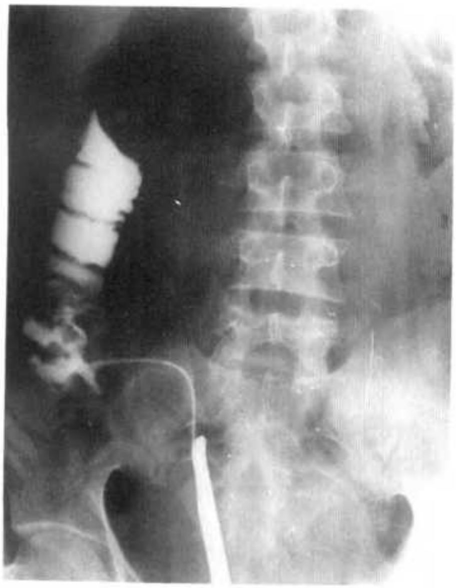

Fig. Retrograde contrast study showing dye in the right colon.

The perineal fistulas were excised down to the urethra. Urethrocystoscopy demonstrated an opening in the right dome of the bladder through which a ureteric catheter could be negotiated and a retrograde contrast study revealed a communication suggesting an appendicovesical fistula (Fig.). This was confirmed at laparotomy. An appendicectomy was carried out together with resection of a cuff of the bladder wall. Histopathology showed chronic appendicitis.

Comment

Since the first reported case of appendicovesical fistula by Keen (1898), 100 cases have been reported (Gabriel and Bryn, 1984). Our patient presented with a periurethral abscess, fistula and a bulbar urethral stricture, but the appendicovesical fistula was silent.

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Chylothorax due to Metastatic Prostatic Carcinoma

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Chylothorax, an uncommon condition, is defined as the pathological accumulation of lymph in the pleural space. In urological practice it is more often associated with testicular carcinoma than with prostatic carcinoma (Bower, 1964; Lifshitz and Rodríguez Ibarra, 1971). The devastating nature of chylothorax requires prompt recognition and agressive management because it causes severe nutritional depletion. We report a classic case of chylothorax due to metastatic prostatic carcinoma in which complete resolution was achieved after bilateral orchiectomy and hormonal therapy.

Case Report

A 78-year-old man with progressive dyspnoea of 2 months' duration was referred with a right pleural effusion. He had had prostatic hyperplasia 10 years previously without obstructive urinary symptoms.

Physical examination showed a right-sided pleural effusion but the heart, abdomen and extremities were normal and at rectal examination the prostate felt hard, suggesting malignancy. A chest X-ray revealed a right pleural effusion, partially loculated. A chest tube was inserted on the right side and milk-like fluid was drained. Cytochemical analysis of the pleural fluid revealed microscopic fat globules, a total protein content of 5.0 g/dl, a triglyceride content of 1800 mg/ml and the white cell count showed 2000 cells/ml with a predominance of lymphocytes. Fungal and bacterial cultures and a search for tumour cells were negative. Serum alkaline and acid phosphatase were both elevated. A radionuclide bone scan was normal.

During the first 5 days in hospital the pleural fluid output was between 4 and 8 l/day. A CT scan of the thorax showed a loculated, massive right pleural effusion (Fig. 1A and B). In order to ligate the thoracic duct, an exploratory thoracotomy was performed and histopathological examination of a mediastinal lymph node revealed malignant metastatic disease of adenocarcinomatous type. The thoracic duct was not ligated because the surgeon was unable to find it; 3 chest tubes were inserted on the right side and over the next 5 days the chylothorax output was between 5 and 10 l/day. The patient's nutritional and general status showed a marked deterioration. Transrectal biopsy of the prostate revealed carcinoma. Bilateral orchiectomy was performed and stilboestrol was given. During the next 48 h the chylothorax output lessened to 150 ml/day and 5 days after orchiectomy an X-ray of the thorax showed partial resolution of the pleural effusion. The serum alkaline and acid phosphatase levels returned to normal. A CT scan of the thorax showed complete disappearance of the chylothorax 57 days after orchiectomy (Fig. 1C and D). The patient was free of symptoms 3 months later and at follow-up 5 months post-operatively there was no evidence of recurrence of the chylothorax.

Comment

This constitutes the fifth case of chylothorax

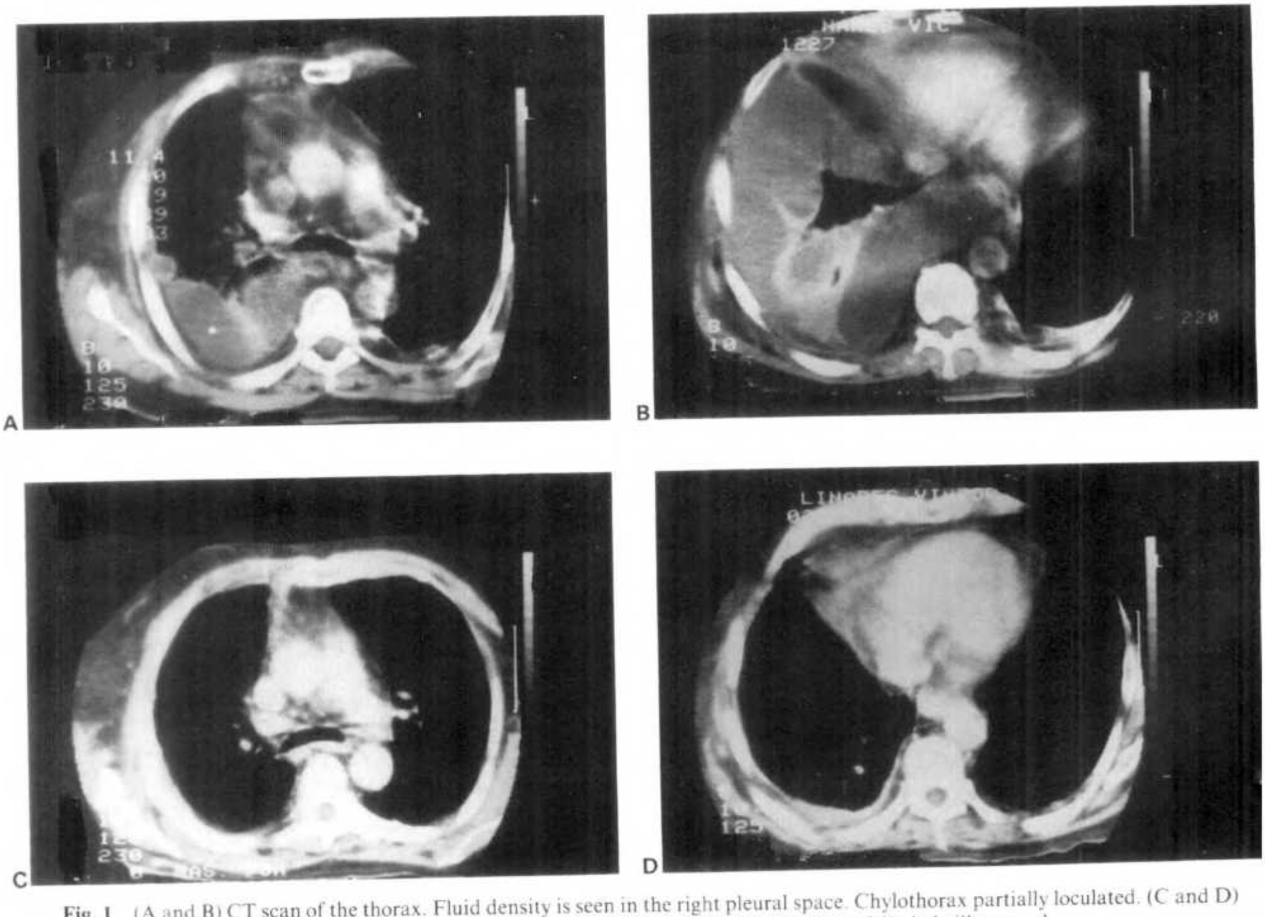

Fig. 1 (A and B) CT scan of the thorax. Fluid density is seen in the right pleural space. Chylothorax partially loculated. (C and D) Pleural fluid has disappeared by the 57th day following orchiectomy and administration of diethylstilboesterol.

associated with metastatic prostatic carcinoma. Little and Walther (1986) reported the successful use of aggressive chemotherapy and adjuvant radiotherapy, but their patient had previously undergone bilateral orchiectomy and treatment with diethylstilboestrol and it is probable that hormonal processes had also been responsible for resolution of the chylothorax.

The management of non-traumatic chylothorax includes ligation of the thoracic duct, pleurodesis, pleurectomy, pleuroperitoneal shunt, pleural scarification and radiotherapy. Early surgery is advocated in the absence of medically treatable disease (Strausser and Flye, 1981). We feel that hormonal therapy can be used in the treatment of chylothorax due to metastatic prostatic carcinoma.

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Requests for reprints to: A. Lifshitz, Departmento de Medicina Interna, Hospital de Especialidades, Centro Medico Nacional IMSS, Aristoteles No. 68, Colonia Polanco CP 11560, Mexico DF, Mexico.

Percutaneous Surgery of the Transplanted Kidney

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Percutaneous surgery is now established in urological practice. We report 2 cases of renal transplants treated by percutaneous methods.

Case Reports

Case 1. A 45-year-old female received a cadaveric renal transplant from a 44-year-old male with no history of renal tract disease. Post-operatively the kidney functioned well and the patient's only problems in the next 3 months were 2 episodes of urinary tract infection. Investigation showed a calculus in the upper ureter causing partial obstruction. Review of an early post-transplant X-ray demonstrated the stone, which was therefore presumed to be of donor origin. Under general anaesthesia the upper pole calix was punctured without difficulty and the tract dilated to 30 F (Fig.). Nephroscopy allowed thorough inspection of the calices, pelvis and upper ureter. The stone was removed and a 28 F nephrostomy tube left *in situ*. This was removed without incident 48 h post-operatively and the patient discharged on the fourth post-operative day.

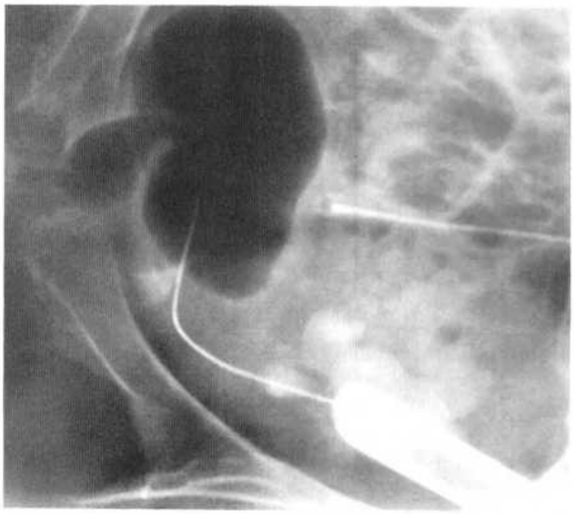

Fig. Amplatz sheath with guide wire inserted past the stone in upper ureter.

Case 2. A 25-year-old male who had had multiple procedures for bladder neck dyssynergia had a renal transplant in 1985. Initially the kidney functioned well, but he later required a clam enterocystoplasty because of high voiding pressures leading to deterioration in renal function. Post-operatively a Cummings nephrostomy tube broke on removal, leaving a 4-cm portion in the renal pelvis. The retained tube was removed percutaneously as described above and the patient left hospital on the fourth post-operative day.

Comment

Renal stones rarely form in transplant kidneys (Mundy *et al.*, 1984) but there have been 2 previous reports of stones being transplanted with the donor kidney (Lerut *et al.*, 1979; Donnelly *et al.*, 1984). While percutaneous investigation of the transplant kidney is well established, there have been few reports of surgical extraction and 1 report of nephroscopy following formal tract dilatation (Hulbert *et al.*, 1985). We found puncture and tract dilatation to be easy. The tract healed rapidly in both patients without significant urinary leakage.

These 2 cases would suggest that percutaneous surgery on transplant kidneys is safe, especially when one considers the difficulties with extensive perirenal fibrosis that are often encountered in transplant patients who have been on cyclosporin.

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Requests for reprints to: I. S. Bailey, Harcourt Villa, Harcourt Terrace, Salisbury, Wiltshire.

A Timely Cystoscopy

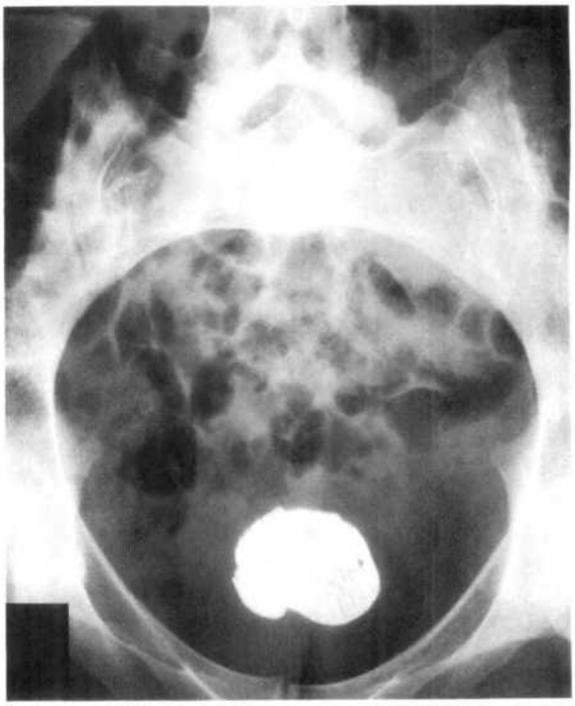
D. J. HICKLING and E. W. LUPTON, *Department of Urology, Withington Hospital, Manchester*, and S. McKEOWN, *Altrincham Priory Hospital, Altrincham*

Self-insertion of urethral or bladder foreign bodies is well recognised but relatively uncommon. When a psychotic patient claims that she has an object in her bladder it is tempting to regard the statement as delusional.

Case Report

A 31-year-old woman was admitted to an acute psychiatric unit under Section II of the Mental Health Act with a history of withdrawn regressive periods during which she was bedridden and enuretic. These were interspersed with disturbed episodes during which she was overactive, violent and hallucinated. Her psychosis improved with treatment but she remained intermittently incontinent and complained that a wrist watch had been inserted into her bladder 3 months previously. On examination an object was palpated through the anterior vaginal wall. A plain abdominal X-ray confirmed the presence of a wrist watch, probably in the bladder (Fig.).

At urethrocystoscopy the urethra was patulous and the bladder lining was oedematous and inflamed. The wrist watch was identified and removed *per urethram* with a small lithotrite. She was dry in hospital for almost 1 month post-operatively.



After discharge home she again complained of incontinence, necessitating protective pads. Urodynamic studies demonstrated a stable bladder with some prolapse but no leakage. She was admitted for assessment of her alleged incontinence but was found to be feigning leakage by dipping her pads into jugs of water.

Comment

Manipulation of foreign bodies into the urethra is usually for sexual gratification (Rada and Jauner, 1982). The objects may be retained in the bladder and subsequent symptoms eventually lead to medical advice being sought. Such patients do not always confess the true nature of the problem. Self-inserted lower urinary tract foreign bodies are more common in men and the objects have included pencils, straws, pens, lipstick tubes, pins and candles (Mitchell, 1968; Frozanpour, 1976).

To our knowledge this is the first reported case of self-manipulation of a wrist watch into the bladder and emphasises the need for suitable investigation, despite the seemingly fantastic claims of the patient.

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Requests for reprints to: E. W. Lupton, Department of Urology, Withington Hospital, Nell Lane, Manchester M20 8LR.

Disappearance of Staghorn Calculi following Withdrawal of Treatment with Acetazolamide

P. E. BEARN, *Department of Surgery, Middlesex Hospital, London*

Case Report

A 59-year-old patient with chronic glaucoma on acetazolamide presented with a 6-month history of urgency and frequency associated with macroscopic haematuria. Renal function, serum and 24-h urinary calcium were normal. Mid-stream urine was sterile.

Plain abdominal radiography (Fig.) demonstrated bilateral staghorn calculi and a large bladder calculus. At IVU both kidneys were seen to excrete normally.

After consultation with ophthalmic colleagues, acetazolamide treatment was withdrawn 1 month prior to the patient's undergoing cystotomy and extraction of the bladder calculus (227 g). Analysis revealed this to be composed of triple phosphate and calcium oxalate.

A repeat plain abdominal radiograph 3 weeks after surgery demonstrated complete radiological disappearance of the staghorn calculi.

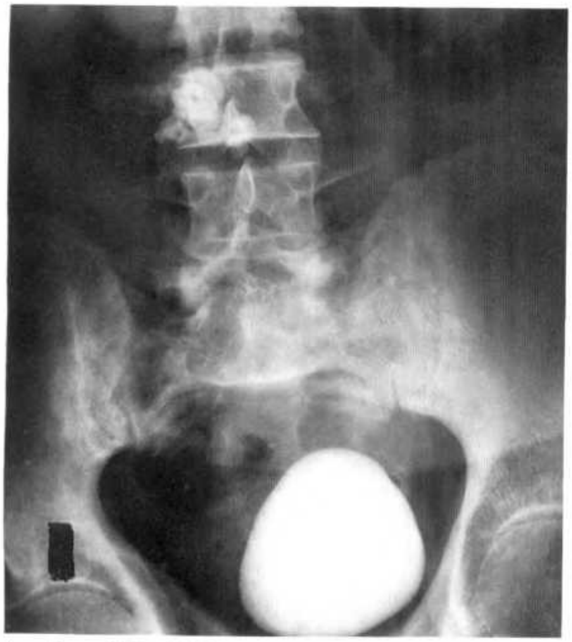

Fig. Control film IVU demonstrating bilateral renal calculi and bladder calculus.

Comment

Acetazolamide is a carbonic anhydrase inhibitor used in the treatment of chronic glaucoma. Its association with urolithiasis is well recognized (Rubenstein and Bucy, 1975; Kass *et al.*, 1981). An important factor is the production of an alkaline urine with a decreased citrate content. This leads to the increased excretion of free calcium which combines with oxalate and phosphate.

This patient's bladder calculus also contained triple phosphate, suggesting a history of urinary tract infections which the patient had not given.

The factors which result in calculus formation are reversible on withdrawal of the drug. The radiological disappearance of staghorn calculi, however, has not been previously reported on its withdrawal. This may be related to leaching-out of calcium into the more acid urine.

This report suggests that when a patient presents with renal calculi whilst on acetazolamide, the drug should be withdrawn before any operative intervention takes place and radiological follow-up undertaken to assess whether the calculus disappears.

Acknowledgement

I thank Mr A. W. R. Williamson, Consultant Urologist, Kent and Sussex Hospital, Tunbridge Wells, for permission to report this case.

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Requests for reprints to: P. E. Bearn, Department of Surgery, Middlesex Hospital, London W1N 8AA.

Lymphatic Cyst of the Penis

S. G. BROOKS and R. E. D. WILLIAMS, *Department of Urology, General Infirmary, Leeds*

We report a case of lymphatic cyst of the penis. As far as we are aware, such a lesion has not been described previously.

Case Report

A 25-year-old white man presented with a 3-week history of an enlarging lump on the dorsum of the penis just proximal to the coronal sulcus. The lesion caused some

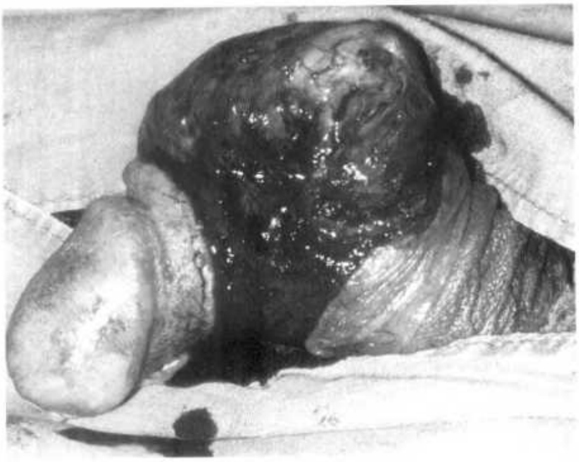

Fig. 1 Appearance of the cyst at operation.

discomfort but no other symptoms. Examination showed a tense, mobile, multiloculated cyst which was partially fixed deeply but not attached to the overlying normal skin. The lesion was excised from between the skin and Buck's fascia (Fig. 1). It measured 3 × 2 cm and contained colourless clear fluid.

Histological examination revealed a space lined by endothelium (Fig. 2) and featuring mural fibrin. Connecting muscular veins exhibited phlebitis and thrombosis. The endothelium stained positively for Factor VIII, implying a vascular origin. There was no evidence of neoplasia.

Comment

The clinical and microscopic features suggested that this lesion was a lymphatic cyst. The mural fibrin deposits were probably secondary to trauma.

All penile cysts are rare. Congenital cysts are lined by epithelium and occur in the midline ventrally (Laurenti and De Dominicis, 1978). Acquired parameatal retention cysts are secondary to urethral gland obstruction, while acquired epidermoid cysts have no specific site and are secondary to trauma.

Other localised lymphatic swellings of the penis have been described. Nonvenereal sclerosing lymphangitis (Nickel and Plumb, 1982) and cystic lymphangioma (Merka *et al.*, 1984) are, however, different clinically and microscopically from the lesion we describe.

Acknowledgement

We are grateful to Dr C. K. Anderson, Consultant Histopathologist, General Infirmary at Leeds, for his advice.

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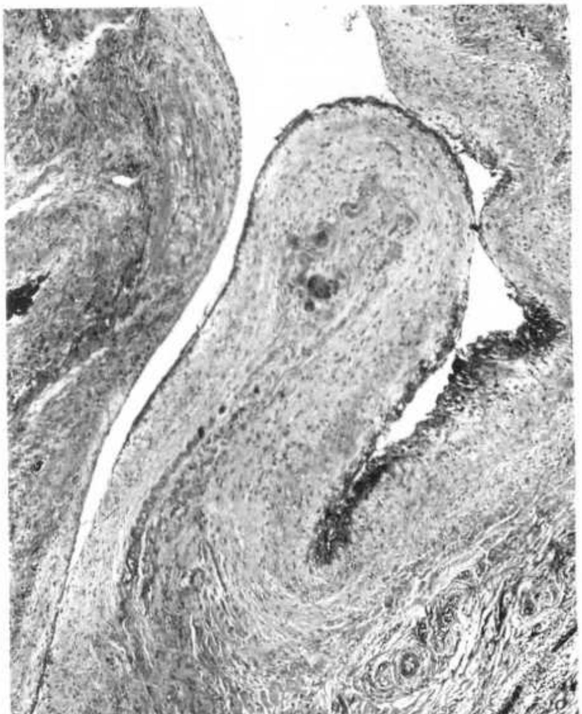

Fig. 2 (A) Lesion removed from the dorsum of the penis with large, endothelial-lined spaces. (H & E × 50). (B) Endothelial-lined space stained for Factor VIII showing positive staining of the endothelium. (PAP × 480).

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Point of Technique

Lithotripsy—a New Treatment for the Impacted Dormia Basket

R. S. COLE, T. G. LISTON and R. C. TIPTAFT, *Lithotripter Centre, St Thomas' Hospital, London*

Case Report

A 65-year-old man was admitted to St Thomas' Hospital with right ureteric colic. An 8 × 4 mm calculus was identified in the right ureter, opposite the ischial spine with moderate dilatation of the right renal pelvis and ureter.

An attempt at Dormia extraction of the stone was made, but the instrument and stone impacted in the intramural ureter. A ureteric meatotomy was then performed, but 3 of the 4 wires of the basket were cut. The Dormia and stone were left *in situ* (Fig.); 48 h later, gentle traction was applied to the remaining Dormia wire under X-ray monitoring, but neither stone nor basket would move. Traction was repeated 3 days later to no avail.

After a further 2 days the stone within the Dormia basket was treated using the Dornier HM3 Lithotripter. Shockwaves (3000 at 22 kV) were delivered via the perineum with the patient in the sitting position on the electrohydraulic hoist. The stone was seen to disintegrate and the basket was retrieved with ease endoscopically. An immediate KUB showed the patient to be free of stone and basket. He made an uneventful recovery.

Comment

The endoscopic removal of a calculus from the ureter with a wire basket is deemed to be worthwhile, effective and safe (Henry and Tomlin, 1975). Occasionally, following engagement of the stone, extraction proves impossible. A proportion of these "impacted" baskets will pass spontaneously but some require intermittent or continuous traction (Carlson, 1950) and others open surgery (Barloon, 1957).

With careful positioning it is possible to localise calculi in the distal ureter with the Dornier HM3 Lithotripter and since January 1987 we have treated 23 such patients. To our knowledge, this is the first time that a stone within an impacted basket has been treated by ESWL.

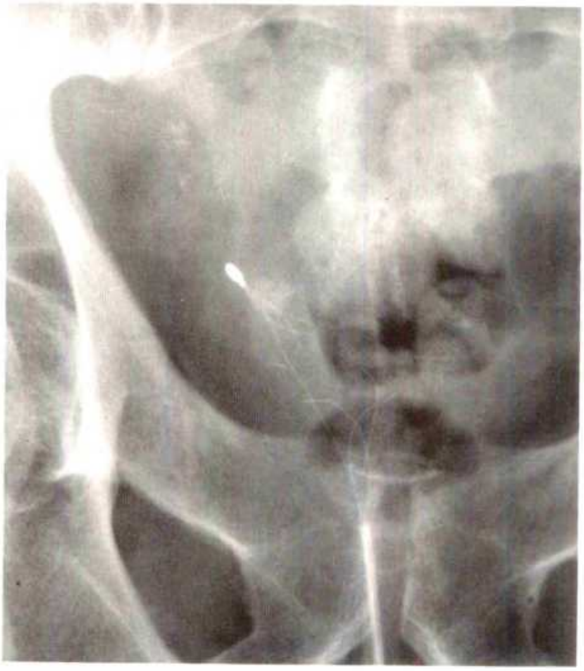

Fig. Plain radiograph demonstrating the disrupted Dormia basket and stone in the distal ureter.

Acknowledgement

We thank Miss Julie Roscoe for typing this manuscript.

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Request for reprints to: R. S. Cole, Lithotripter Centre, St Thomas' Hospital, London SE1 7EH.

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Correspondence

re Bulbocavernosus reflex latency in the investigation of diabetic impotence. B. T. Parys *et al. Br. J. Urol.*, **61**, 59–62, 1988.

Letter to the Editor. We too have studied a group of 24 impotent diabetic men by means of the bulbocavernosus reflex (BCR) and pudendal evoked responses (PER). This group of patients was compared with 8 potent diabetic men and with 14 healthy, potent men.

We found that the mean penile cutaneous sensory threshold was statistically significantly increased in impotent diabetic men (mean 54.37 v) compared with normal subjects (mean 22.5 v) but was also increased significantly in potent diabetic men (mean 48.1 v) ($P<0.01$, Wilcoxon's test). Furthermore, no statistically significant difference was observed in their mean BCR latencies (impotent 40.7 ms ± 9.1; potent 35 ms ± 3.77; normals 34.7 ms ± 2.9) or PER latencies (impotent 44.7 ms ± 7.5; potent 45.6 ms ± 4.5; normals 41.67 ms ± 2.5).

As a confirmation of a pudendal neuropathy, BCR and PER are useful investigations when extensive revascularisation procedures, for example, are to be considered in diabetic impotent men. Although part of the statement of potency could be subjective in our 8 potent diabetic men, abnormalities in the RBC and PER responses do not seem to be specific, as they could be found in diabetic men with no sexual problem. Thus we agree with the conclusion of Desai *et al.* (1988) that RBC, and in our study PER, are not reliable in determining the cause of diabetic impotence and that further specific tests are needed to investigate pelvic autonomic neuropathy.

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1070 Brussels,
Belgium.

Reference

Desai, K. M., Dembny, K., Morgan, Hilary *et al.* (1988). Neurophysiological investigation of diabetic impotence. Are sacral response studies of value? *Br. J. Urol.*, **61**, 68–73.

Reply by B. T. Parys and K. F. Parsons. The results quoted by Dr Herbaut *et al.* imply the presence of a suprasacral abnormality in their patients, the reflex latencies being normal with elevation of the sensory thresholds (Galloway *et al.*, 1985). We agree that BCRL and SRLs are not as specific to the mechanisms of erection as is desirable, but do help to select the initial dose of intracorporeal papaverine, as care must be taken not to produce avoidable priapism, which is commoner in neuropathic impotence.

Reference

Galloway, N. T. M., Chisholm, G. D. and McInnes, A. (1985). Patterns and significance of the sacral evoked response (the urologist's knee jerk). *Br. J. Urol.*, **57**, 145–147.

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. St Helier, Jersey, Channel Islands. 20–23 June 1989

All correspondence to: Hugh N. Whitfield, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

Shackman Travelling Fellowship 1990

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1989.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

International Consensus Conference on Prostate and Testicular Cancer

Hull. 12–15 April 1989

Further information from: D. W. W. Newling, 21 Albion Street, Hull HU1 3TG.

Edinburgh Urological Festival

A Joint Postgraduate Urological Meeting: Edinburgh University Department of Surgery (WGH) and Department of Urology, University of California, Davis

Edinburgh. 23–26 August 1989

The programme will consist of review lectures by invited speakers from the USA and Europe, with short papers by participants on the following topics: Superficial Bladder Cancer; Bladder Dysfunction; Reconstructive Surgery; Infertility and Sexual Dysfunction; Neo-adjuvant Chemotherapy, Flow Cytometry in Urology.

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK *or* Professor A. Stone, Department of Urology, University of California, Davis, Sacramento, USA.

Ghent's Urethral Surgery Day

Ghent, Belgium. 14 April 1989

Live demonstrations will be given of urethral reconstructive surgery (hypospadias, strictures, etc).

Further information from: Professor W. A. De Sy, Department of Urology, University Hospital, 9000 Ghent, Belgium.

Seventh International Symposium of Radionuclides in Nephro-urology

Williamsburg, USA. 7–10 May 1989

Topics for discussion include hypertension, renal physiology, radiopharmaceuticals, renal function, renal imaging, metabolic disease, transplantation, paediatrics and urological diseases.

Further particulars from: Dr M. Donald Blaufox, Department of Nuclear Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.

54th Congress of the Belgian Society of Urology

Brussels, Belgium. 27–28 May 1989

The topic will be "Lower Urinary and Genital Pathology in Children."

Further particulars from: Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.

XVIIIth Annual Conference of the European Dialysis and Transplant Nurses Association—European Renal Care Association

Göteborg, Sweden. 11–14 June 1989

XXVIth Congress of the European Dialysis and Transplant Association—European Renal Association

Göteborg, Sweden. 11–15 June 1989

Further information from: General and Scientific Secretariat, Transplant Unit, Department of Surgery, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

Canadian Urological Association

Quebec City, Canada 18–22 June 1989

Further information from: Dr J. P. Collins, B–3, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.

S.U.W.O. (Urological Research Foundation) Symposium on Paediatric Urology

Rotterdam, The Netherlands, 30 June and 1 July 1989

The following topics will be discussed: ureteric obstruction, duplication of kidney and ureter, neurogenic bladder dysfunction, anorectal malformation and vesicoureteric reflux.

Further information from: Mrs S. Wolff, Department of Urology, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

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Book Reviews

Percutaneous Renal Surgery. Second edition. By S. R. Payne and D. R. Webb. Pp. 153. Edinburgh, London, Melbourne, New York: Churchill Livingstone. 1988. Price £29.50.

The first edition of this book was published in 1983, since when the principles of percutaneous surgery have not changed, but techniques and instruments have been refined and new applications explored. In addition, extracorporeal shock wave lithotripsy has arrived on a large scale since the first edition.

The book is divided into three parts concerning anatomy and access, instruments and techniques. In addition, there are appendices setting out the exact equipment required for various procedures. The last appendix describes the technique best suited for the treatment of calculi in various parts of the urinary tract.

The book will be particularly useful for surgeons beginning percutaneous surgery as it is clearly written, with good diagrams and photographs. The descriptions of renal anatomy and equipment are particularly good. Inevitably, the authors tend to write best on the techniques they have practised and they tend to be dismissive of others, for example tract dilatation using balloons and flexible ureteroscopy. Whilst not primarily about ESWL, the two techniques are inexorably connected and the chapter on the role of endourology in combination with ESWL is disappointing and somewhat out of date

Early ideas that percutaneous surgery would be superseded by ESWL have proved incorrect, assuring this authoritative book an important place and, it is hoped, many future editions.

Uremic Toxins. (Advances in Experimental Medicine and Biology). Volume 23. Edited by S. Ringoir, R. Vanholder and S. G. Massry. Pp. 296. New York, London: Plenum Press. 1988. Price US$59.50.

This book forms the Proceedings of a meeting held in October 1986 in Belgium and provides an international view of what is meant by the term "uraemia". The papers are published in the style in which they were submitted, so there is a variety of typefaces and of presentation. Some detailed biochemical papers are almost entirely without illustrations, which makes them unintelligible to the non-specialist Several papers go over well rehearsed ground, *e.g.* the toxicity of parathyroid hormone, hippuric acid, purine metabolites and aluminium. Some of these problems have been solved at least on a clinical level There are a number of other papers which describe the adverse effects of fractions of uraemic serum on numerous indices of cellular function. The volume closes with a collection of papers which describe the use of urea kinetics and mathematical modelling to prescribe dialysis, and some esoteric methods of dialysis aimed at improving uraemic toxicity.

This is very much a book for a specialist unit. Although some of the papers are interesting, one is left with the unhappy feeling that uraemia is still poorly understood.

Progress in Infertility. Third edition. Edited by S. J. Behrman, R. W. Kistner and G. W. Patton, Jr. Pp. xvi + 852. Boston, Toronto: Little, Brown and Co. 1988. Price £65.00.

The title of this book is apt. There has been an explosion in our understanding of human reproduction following the world-wide use of IVF and other similar techniques. The main impact of IVF has been to crystallise our understanding of the control of the menstrual cycle and ways to induce and monitor ovulation, more important to the urologist, IVF has opened the door to a much more detailed study of sperm. In this book there are comprehensive chapters on both of these aspects. It is doubtful if many urologists will buy the book, but it is a useful reference for those centres specialising in the treatment of the infertile couple, especially if the laboratory techniques available involve more than just standard semen analysis.

Nephrology. (Mainstream Medicine Series). By A. M. Davison. Pp. viii + 374. London: Heinemann Medical Books. 1988. Price: £12.95.

An excellent small book aimed at postgraduates preparing for examinations—including trainee surgeons. One third of this book is on renal failure in its various forms, dialysis and transplantation and urinary tract infections. Urologists need a general knowledge of nephrology and this book gives a good up-to-date coverage of the subject.

Pediatric and Adult Reconstructive Urologic Surgery. Second edition Edited by J. A. Libertino. Pp. xviii + 692. Baltimore, London, Los Angeles, Sydney: Williams and Wilkins. 1987. Price £97.00.

The first edition of this book, in 1977, contained 320 pages, the second edition has 690. The first edition was comprehensive and well illustrated, the second edition is even more so. It is tempting to wonder whether the designation of reconstruction is any longer correct or whether this is a textbook of urological surgery with all but the basic operative procedures and, of course, excluding endoscopic urology.

Few of the procedures described are common and many are complex and rare, but even those who profess a special interest in reconstructive urology would have only a proportion of these techniques in their repertoire.

Apart from the endoscopic treatment of urethral strictures the contents are true to the title and will appeal to all urologists because of the clear descriptions of a very wide range of operative procedures. One quibble: some of the excellent illustrations are rather small, but no space is wasted in the book, which is packed with useful material. This is an excellent and authoritative reference source

Current Therapy in Genitourinary Surgery. Edited by M. I. Resnick and E. Kursh. Pp. xxvi+496. Toronto, Philadelphia: B. C. Decker Inc. 1987. Price £50.50.

This book is one of a series that covers many aspects of medicine, surgery, orthopaedics, critical care, anaesthesia and so on. The format is very interesting and should attract a wide readership—it is, to quote from the preface, "a compilation of opinions as expressed by respected authorities in the field who clearly state why certain procedures or treatment patterns are followed". Each contribution is short and sharp—rarely more than 4 to 6 pages and there are no references. This is an excellent reference source and is comprehensive. The book would prove very useful to have in any urological unit or department.

New Techniques in Urology. Edited by R. W. DeVere White and J. M. Palmer. Pp. xiii+431. New York: Futura Publishing Co. 1987. Price US$65.00.

This novel title reflects the remarkable impact of new technology on urological surgery. Of the techniques described in 28 chapters, less than a handful were in existence and properly available to urologists 10 years ago. The book is in four parts—renal calculi, new instrumentation in urology, diagnosis and new technologies in patient management. Amongst the new techniques in the management of renal calculi it was a surprise to find there is still a place for renal pelvic perfusion with Renacidin (using a loop nephrostomy, the originator of which, Mr G. Tresidder, seems now forgotten). New instrumentation includes MRI, lasers, quantitative cytology and cystometry A particular interest of one of the editors is flow cytometry and there is an excellent review of this subject. The main emphasis in the section on diagnosis is on ultrasound, including an evaluation of the fetus with hydronephrosis. The chapter on ultrasound and evaluation of the prostate is cautious and emphasis the unacceptably high false-positive rate (for prosta cancer) and the difficulty in interpreting abnorm findings. On the basis of current data, some enthusias for this technique would question these and oth opinions The section on new technologies is diverse ar very interesting—ranging from sperm penetration ass to nutritional support

This book is full of material that represents all of tl major discussion points in urology. It is good value and recommended to all urologists.

Urogenital Infections. New Developments in Lab ratory Diagnosis and Treatment. (Advances Experimental Medicine and Biology). Volume 2 Edited by A. Bondi, D. D. Stieritz, J. M. Camp and Linda Ann Miller. Pp. 146. New York, Londo Plenum Press. 1988. Price US$45.00.

Genitourinary specimens comprise a large portion of tl work of most clinical microbiology laboratories. Th annual symposium provides detailed information c procedures and therapy. The topics include definitions types of urinary tract infection, significance of posit cultures, differentiation of lower and upper tract infe tion, automated culture and other techniques, specificit sensitivity and predictive values of culture results, an murine models of infection. Consideration is given to tl role of host factors in infection, such as the large numb of pilus receptors found in the cells of subjects of F phenotype and the formation of adhesins, especially pili, by *Escherichia coli.*

The diagnosis of *Chlamydia* infections poses problen of specificity and sensitivity of currently used ELIS techniques. Culture yields varying numbers of fal negative results and is expensive. The role of DN homology testing is an exciting prospect for the futu and is discussed fully in relation to the use of no radioactive markers such as biotin covalently bonded deoxyuridine triphosphate

Mycoplasma hominis and *Ureaplasma urealyticum* a neglected pathogens requiring greater consideratio Their part in disorders of reproduction is described detail. The importance of *Gardnerella vaginalis* and tl role of associated *mobiluncus* strains is still a matter f disagreement.

This text contains a wealth of useful information interest to both laboratory workers and urologis involved in problems of genitourinary tract infection.